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SUBDURAL HÆMORRHAGE, CYSTS AND FALSE MEMBRANES: ILLUSTRATING THE INFLUENCE OF INTRINSIC FACTORS IN DISEASE WHEN DEVELOPMENT OF THE BODY IS NORMAL.

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INTRODUCTION.

WHEN considering intrinsic factors in disease two main subdivisions must be recognized: (1) intrinsic factors related to anatomical structures whose development has been normal; and (2) intrinsic factors related to anatomical structures whose development has been abnormal.

The *Bacterium typhosum* finds conditions suitable for its multiplication in the lymphoid tissue of the small intestine, whereas the bacteria of the dysentery group find these conditions in the mucous membrane of the large intestine. The *Neisseria meningitidis*, whose normal habitat is the nasopharynx, is believed by many authorities to reach the meninges by way of the blood-stream, and not by the direct route through the cribriform plate. *N. meningitidis* in the blood finds suitable conditions for multiplication in the meshes of the pia-arachnoid. The reasons for the multiplication of pathogenic bacteria in different sites in the body are obscure. The same is true with neoplasms as with infections. When there is widespread involvement of the skeleton by carcinoma which has arisen in, say, prostate or mamma, presumably the cancer cells are widely disseminated not only in bones of the skeleton but in many other tissues of the body, yet these other tissues may remain relatively or absolutely free from involvement by carcinomatous metastases.

These are two examples which suggest that tissues do not all behave alike when bacteria or tumour cells enter them or become closely related to them. These conditions, though not understood, are generally recog-

[1]Much of this work, in its early stages, was conducted at the Kanematsu Institute of Pathology, Sydney Hospital, Sydney, Australia.

nized to exist. In the present paper, what is thought to be a third example of special behaviour of normal tissue is described. The two examples mentioned above relate to the behaviour of normal tissues to pathological elements, namely bacteria and cancer cells, but this third example relates to the behaviour of normal tissues to the presence of blood.

When blood clots in a blood-vessel, for example thrombosed hæmorrhoids, the clot becomes organized and converted into fibrous tissue. The organizing clot and the cicatricial tissue when it forms are adherent to the wall of the vessel. The same takes place when a clot forms in an artery. When a study is made of the behaviour of blood in the subdural space (the barrier between neural and non-neural tissue being maintained) a different state of affairs is found. Blood-vessels and cells of connective tissue origin pass into the clot from the dura mater, and later the clot becomes organized; however at no stage is there firm union of the new tissue with the under surface of the dura mater. The organized tissue is very loosely attached to the under surface of the dura mater by occasional, relatively delicate, blood-vessels. This curious form of reaction is responsible for several unusual pathological and clinical effects.

Historical Sketch.

(1) *Subdural Hæmorrhage in Adults.*

Subdural lesions of the kind to be discussed in this paper have been referred to under many different titles, the variety of names being in keeping with the numerous opinions that have been expressed as to the nature and ætiology of this interesting condition.

Ford Robertson (1900), who used the term subdural false membrane, gave the following list of descriptive titles that had been employed up to then by different writers: hæmatoma duræ matris, pachymeningitis hæmorrhagica interna, meningeal hæmorrhage, arachnoid cysts, false membranes of the arachnoid, meningeal apoplexy, blood cyst of the dura mater, subdural hæmatoma, false membranes under the dura mater and subdural membrane. Virchow (1857) was the first to describe in detail the histological character of subdural false membrane, though the condition had been recognized long before his time. Putnam (1925) speaking of Virchow (1857, 1863) said "he recognized the possibility that a subdural hæmorrhage might occur from trauma to large vessels or might burst through the pia from the cerebral cortex, or might even occur spontaneously in hæmorrhagic, valvular or vascular disease. But the structure formed in such a way, he believed, probably would not reproduce the

appearance or behaviour of the spontaneous hæmatoma. He did not describe any histologic difference between the two, but supposed that there must be one because fresh points of hæmorrhage are seen in even old membranes, which suggests that they are progressive, and the clinical symptoms are chronic and intermittent. The sequence of events he believed to be as follows: In certain patients, especially in the insane, the dura becomes chronically inflamed, as is shown by the exudation of a thin film of fibrin, sometimes tinged with blood, over its inner surface. Capillaries grow into this from the sparse vessels of the dura and, if conditions of its formation repeat themselves, another layer of fibrin may form and become organized. The new tissue may be so vascular 'that scarcely any other form of tumour is to be compared with it.' The vessels are very large, thin-walled and irregular. Under the influence of hyperæmia, they may rupture, producing small ecchymoses which absorb, leaving pigment behind them; or the separation of layers of the membrane may tear other capillaries and give rise to massive hæmorrhages. These in turn become similarly organized and their capillaries may rupture. He gave the name pachymeningitis interna chronica to the fibrinous exudation and its organization; if extravasation were a prominent feature of the tissue, he called it pachymeningitis hæmorrhagica. The bloody sacs or cysts he called hæmatomas of the dura. He recognized that the hæmorrhagic contents of the cyst might become replaced by serum (hygroma of the dura), and considered this one of the forms of external hydrocephalus."

Rindfleisch (1873) said that hæmorrhagic pachymeningitis begins with a hyperæmia which manifests itself as a barely perceptible rosy flush of the internal surface of the membrane, usually so white and smooth; throughout the entire course of the disease, it remains stationary at this insignificant level. All the more remarkable are the changes which are developed on the surface of the dura mater in connexion with this hyperæmia. The naked eye observes, first of all, a lax, gauzy, yellowish efflorescence, studded with innumerable bloody points. This may readily be peeled off with the forceps, and if, while doing this, we fix our attention upon the line along which separation is taking place, we notice here and there, reddish threads stretched out between the dura mater and the false membrane, which are forthwith torn across. These threads are simply blood-vessels, passing from the dura mater into the false membrane, where they break up into stellate ramifications.

Speaking of those intercurrent hæmorrhages which play so prominent a part in the clinical history of pachymeningitis, Rindfleisch said it is

self-evident that the arrangement of the vessels in the false membrane must almost inevitably lead to their rupture. Even the thinnest efflorescences, therefore, are usually studded with bloody points. The thicker the false membrane becomes, the larger grow the hæmorrhages, until at last we find those pools of blood, as broad and thick as a man's hand. All these extravasations are interstitial.

Huguenin (1877), Putnam said, reverted to the "hæmorrhagic" theory of origin. For Huguenin, the thin fibrosanguineous subdural layer was a hæmorrhage and the resulting vascularization was merely the organization of a clot. He agreed that subsequent hæmorrhage could occur from rupture of dilated capillaries, and that it was invariably within the membrane previously formed.

Wigglesworth (1892) also supported the hæmorrhagic theory. Referring to statements in favour of the inflammatory theory he said: "All these descriptions start with the assumption that the primary thing is an inflammatory exudation upon the inner surface of the dura mater, and that the hæmorrhagic element met with is a secondary result of the rupture of newly-formed vessels in this inflammatory membrane. I take exactly the opposite view to this, and contend that the membranes found adherent to the inner surface of the dura mater . . . are all the direct result of hæmorrhagic effusions into the subdural space (arachnoid cavity); and that any inflammatory changes which may be met with in the dura mater, are purely secondary and due to the irritation set up by the effused blood."

Middlemass and Ford Robertson (1894) recognized two classes of cases; those which are the direct outcome of a widespread morbid process in the substance of the dura mater itself, the true subdural membrane formation of the insane, and those that are produced as a result of hæmorrhage into the subdural space, from, it may be, one point, or, more rarely, several points. In the first class, comprising the true subdural membranes of the insane, the earliest changes found in the dura consist primarily in a hyaline degeneration of the vessels, and their perivascular canals, which leads to obliteration of both. While the vessels are undergoing this morbid change, small hæmorrhages frequently occur from them. Their obliteration is followed by the formation of new capillaries. The authors stressed the fact that in these true subdural membranes of the insane all signs of inflammatory reaction are absent in the early stages of the membrane formation. They did not agree with Virchow who regarded the disease as primarily inflammatory but considered that it results from degenerative changes which occur in the dura mater.

As to the immediate cause of the degenerative changes they were unable to speak very definitely. The most marked manifestation of the second class, they said, is a large recent blood clot in the subdural space, the hæmorrhage most frequently having occurred from a minute opening in one of the pial veins.

Trotter (1914) thought the hæmorrhages in his cases entirely and solely of traumatic origin; one reason given for this view was the fact that in two cases complete recovery followed drainage of the hæmorrhage with no residual symptoms of any kind, and that there was no tendency whatever to recurrence of symptoms after six months and five years respectively.

Of the four cases on which he had operated the hæmorrhage was bilateral in two; from the slowness of its course and the insidious onset of the symptoms Trotter thought that there could be little doubt that the bleeding was of venous origin and considered it nearly certain that the cerebral veins passing from the brain to the tributaries of the superior longitudinal sinus were always the source of the blood. According to Trotter there are no signs of inflammation and no adhesions surrounding the cyst, the wall of which seems to be formed entirely by clotting and organization of the peripheral layers of blood; he thought it possible that the arachnoid contributes to the inner wall of the cyst.

Putnam (1925) published a paper on "Chronic Subdural Hæmatoma" based on eleven cases and including a comprehensive review of the literature. He said "The enveloping membrane on the side toward the arachnoid is thin and covered with mesothelium. On the dural side, it is more dense and composed of organizing granulation tissue containing large mesothelium lined spaces containing blood and fibrin which appear to anastomose with each other and with the capillaries. In this respect, the membrane of the traumatic hæmatoma seemingly differs from that of the commonly described pachymeningitis hæmorrhagica interna, in which the thin-walled vessels are enormous, and no mesothelium lined spaces are seen. Such a pachymeningitic membrane may possibly give rise to hæmatomas, which symptomatically and in the gross resemble the post-traumatic variety. In certain cases in which the onset of symptoms is delayed for only a few days after trauma, it is possible that they may be due to a hæmatoma formed immediately but which only announces its presence when the brain becomes œdematous or congested. In other cases the occurrence of late hæmorrhages seems probable and may be due to the formation of communication between the mesothelium lined spaces and blood-vessels, with rupture of one or the other."

Cushing (1925) considered that the subdural hæmatoma is encapsulated by mesothelial cells of the arachnoid.

Russell and Cairns (1934) studied subdural false membrane or hæmatoma in carcinomatosis and sarcomatosis of the dura mater. They said that study of the microscopic appearances in their series of cases showed that the membrane forms within the areolar layer of the dura mater, and histological examination showed that "the membrane, though tending to be detached so easily from the overlying dense dura, was actually nothing more than a greatly thickened areolar layer of the dura." They concluded that, in the cases they described, the subdural false membrane was the result of mechanical interference with the circulation by permeation of veins and capillaries with growth.

Hanna (1936) said the dura has three distinct fibrous layers, and that, situated between the two innermost layers, is a dense capillary bed. He thought that, in true chronic subdural hæmorrhage, the point of origin of the hæmorrhage is either intradural or into newly formed membranes, and not a ruptured superior cerebral vein.

Kaump and Love (1938) considered that subdural hæmatomas occur intradurally in the middle vascular layer of the dura. While they admitted the possibility of the existence of a true subdural collection of blood, they stressed the point that most such lesions are intradural in character.

Baker (1938) expressed the opinion that in most cases the subdural hæmatoma is really an intradural bleeding, the hæmorrhage occurring from the two layers of dural capillaries and splitting off a portion of the original pachymeninx, which acts as the inner limiting membrane to the coagulum.

Leary (1939) presented evidence to prove that massive subdural hæmorrhages are actually subdural and not intradural. The common source of subdural hæmorrhages, he stated, is ruptured bridging veins. He said that "minor hæmorrhages with relation to the dura or the subdural space have no clinical significance, do not constitute hæmatomas and can be excluded." He also stated "The group of subdural hæmorrhages which has clinical importance is made up of relatively massive hæmorrhages. Failure to differentiate these massive hæmorrhages from the minor petechial or conglomerate petechial hæmorrhages into the dura serves but to complicate and confuse the issue." Leary believed that "the persistence which is the outstanding characteristic of subdural hæmorrhages as compared with hæmorrhages elsewhere in the body arises from the fact that the burden of organizing and removing the

clot is thrown on a poorly vascularized dense connective tissue membrane that is in contact with only one surface of the clot and has difficulty in carrying out the assignment. In serous spaces organization of clot proceeds from all surfaces. Here the effort at repair is from one surface alone."

Leary added that: "When in fracture of the skull there is laceration of the brain, the blood which accumulates in the subdural space is removed with relative rapidity through the efficient arachnoid drainage system. As a result, chronic subdural hæmatoma does not arise under these conditions. An unbroken arachnoid appears to be a necessary element in the production of subdural hematoma."

(2) *Subdural Hæmorrhage in Children and in the Fœtus.*

Sutherland (1894) reported two cases of subdural hæmorrhage associated with scurvy, one in a patient aged 14 months and one in a patient aged 24 months.

Burhans and Gerstenberger (1923) stated that internal hæmorrhagic pachymeningitis occurring in children cannot be considered a rare disease. Of their five cases only one was examined post mortem. From the standpoint of ætiology, syphilis and diphtheria could be excluded in every instance except one in which syphilis might by some be considered to have been a possible factor. They thought that trauma at birth or later or both was the most important ætiological factor in their cases.

Debré and Semelaigne (1926) said it seemed to them difficult to confuse clinically the meningeal hæmorrhages of obstetrical origin and the meningeal hæmorrhages due to the pachymeningitis. They considered that, in the genesis of hæmorrhagic pachymeningitis, syphilis plays an important if not a unique part.

Chase (1930) said subdural hæmorrhage is *the* important intracranial lesion in most cases of birth trauma. The subdural hæmorrhage is largely supratentorial and often bilateral. It is usually due to a stretching and rupturing of the small tributaries of the great cerebral vein near its junction with the straight sinus. Tentorial splits are relatively more numerous in the premature than in the full-term infant, partly because of the greater immaturity of fibres of the dural septa in prematurity.

Sherwood (1930) recorded nine cases of chronic subdural hæmatoma in infants. Previous infection had been present in some of the cases, but this observation was not constant enough to be of importance. Two patients had had otitis media, one pneumonia and one tonsillitis. Sepsis, thought to be secondary, was present in one case. Rickets was present in one

case but no history of trauma could be elicited in any of the nine. A syphilitic process was present in one case, and a suspicion of it in another. Sherwood concluded that the ætiology in infants remains obscure; no one factor was found to account for every case, and it seems likely that the condition can occur as a result of more than one cause.

Pigeaud (1928) studied meningeal hæmorrhages in three fœtuses of from four to five months. As the fœtuses were situated in intact sacs containing amniotic fluid they almost certainly came from spontaneous abortions and had been preserved from traumatism since their expulsion. Subdural hæmorrhage was present in all three. In two of the cases macrophages charged with iron containing pigment indicated that the hæmorrhage had preceded death of the fœtus. Pigeaud thought the evidence favoured an infectious ætiology and tended to incriminate syphilis.

(3) *Subdural Hæmorrhage Associated with Aplasia of the Brain and with Atrophy of the Brain.*

(*a*) Sutherland and Paterson (1913) published a paper on a type of cerebral maldevelopment (fore-brain aplasia). Post mortem their two cases were very similar. On opening the skull a quantity of fluid escaped, amber coloured in the first case, definitely blood-stained in the other. The amount of fluid was about half a pint, and it occupied the cavity of the pia-arachnoid membrane (external hydrocephalus). The arachnoid surface of the dura mater was soft, and perhaps slightly thickened (? from deposition of a new layer). In one case there were hæmorrhagic patches in the parietal region of the dura. The brain lying on the base of the skull was very small and covered with œdematous-looking pia-arachnoid. Two views were considered: (1) That there had been pachymeningitis with proliferation of the meningo-vascular tissue and secondary cerebral involvement; (2) that there was a primary aplasia of the cerebral tissue with secondary meningo-vascular proliferation. The second view was supported by Gordon Holmes.

(*b*) Fleming and Cookson (1925) reported a case of multiple neurofibromata associated with a true angio-neurofibroma of the acoustic nerve, Jacksonian epilepsy and osteoporosis. The cranial vault when cut into was very soft. None of the other bones showed marked softening. The dura mater was adherent to the bone over considerable areas. The whole of the dura mater was much thickened and discoloured, there being a well-marked pachymeningitis hæmorrhagica interna. There was considerable general atrophy of the frontal and parietal regions of the brain, and endotheliomata of the meninges were present.

(4) *Subdural Cysts.*

Bowlby (1900), speaking of hæmorrhage into the arachnoid cavity (by which he meant subdural hæmorrhage), stated that in those cases where the lesion is not a fatal one, the extravasated blood may either become absorbed or encysted. The retention of the blood in the arachnoid sac, he said, may be productive of serious symptoms of cerebral irritation, and in some recorded cases of insanity. On the other hand, Bowlby said, he had, quite by chance, found a blood cyst in the arachnoid (by which he meant subdural space) as large as a hen's egg in a patient who never complained of any head symptoms at all, and in whom he could obtain no history of severe injury.

Barratt (1900) published a report on a subdural blood cyst in a male 57 years of age who had been subject to headaches all his life. Post mortem the dura was adherent to the skull-cap and exhibited on its inner surface a thin yellowish-brown pellicle at the base and on the left side over the vertex, while on the right side a large moderately firm flattened sac of a dark reddish-brown colour lay in the subdural space over the cerebral hemisphere, which was considerably flattened. At the edges the sac thinned off and became continuous with the rusty pellicle already referred to. The pia-arachnoid was slightly thickened and opaque, chiefly over the vertex. The subarachnoid space contained clear yellowish fluid, and the sulci lying between the cerebral convolutions were widened. The gyri were wasted. The ventricles like the subarachnoid space were somewhat dilated. The spinal cord showed some degeneration in the crossed pyramidal tracts, especially on the left side.

Barratt concluded that two morbid processes were present within the skull cavity, first atrophy and wasting of the brain with opacity of the pia-arachnoid and fluid distension of the sub-arachnoid space and ventricles, such as is commonly found in asylum patients advanced in life, suffering from dementia, and secondly a subdural cyst with well-formed wall and partly fluid contents. He found difficulty in deciding how far the clinical symptoms should be attributed to the first and how far to the second condition.

Zollinger and Gross (1934), when discussing the late onset of pressure symptoms resulting from traumatic subdural hæmatoma, said: "It has been generally agreed that the delayed onset of clinical symptoms is dependent on an augmentation in volume of the blood that is entrapped in the subdural space. Some clinicians believe that repeated bleeding accounts for enlargement of the subdural hæmorrhage, but there is little pathologic evidence to support this view in the majority of cases.

"Gardner recently showed that the sac which forms about such a collection of blood has the characteristics of a semi-permeable membrane. He believed that the enlargement of the sac depended on the passage of tissue fluids into the hæmatoma as a result of differential osmotic tension existing between whole blood and cerebrospinal fluid when they are separated by a semipermeable membrane. Gardner stated that the fluid which entered the subdural hæmatoma was derived from the surrounding tissues and particularly the cerebrospinal fluid. It would seem likely, however, that the added substance may come in part from the plasma of the circulating blood." The authors considered that the wall of a subdural hæmatoma acts as a semipermeable membrane, that blood within a subdural hæmatoma breaks down slowly over a period of months, that disintegration of blood produces a great rise in its effective osmotic pressure, and blood within a hæmatoma is progressively diluted. "The resultant augmentation in size of the lesion causes rising intracranial pressure and progressive clinical symptoms. The late onset of symptoms is therefore directly dependent on the slow disintegration of red blood cells encapsulated within the hæmatoma membrane."

(5) *Experimental Investigations of Subdural Hæmorrhage and False Membranes.*

Barratt (1902) said experimental implantation of false membrane into the subdural space of cats fails to set up a progressive process of membrane formation. The few changes which occur outside the operation area are comparable to a process of repair.

Marie, Roussy and Laroche (1913), faced with the inconstant results of experimental reproduction of pachymeningitis hæmorrhagica in animals, undertook a series of researches in the rabbit and the dog. They injected under the dura mater, in the rolandic area, pure blood, blood to which had been added staphylococci heated for half an hour at 56° or an irritating mixture composed of fatty acids and nucleinate of soda. From the results of these experiments they concluded that aseptic blood does not constitute an irritant capable of establishing on the meninges an inflammatory reaction durable enough to end in pachymeningitis hæmorrhagica, and were opposed to the theory that primary hæmorrhage determines the pachymeningitis. On the other hand blood to which microbes of low virulence or irritating substances have been added can bring about the lesions of pachymeningitis which may become hæmorrhagic and resemble those observed in man at the commencement of the pachymeningitic process.

Putnam and Putnam (1927), when referring to experimental investigation of subdural hæmorrhage, stated that as similar experiments had led to diametrically opposite conclusions in the hands of various observers, it seemed worth while to repeat them under as rigid control as possible. Fifteen cats and three dogs were operated on, and blood injected beneath the dura mater. The authors concluded that apparently a true, progressive chronic hæmatoma of the dura has never been produced experimentally. The lesions seen after the subdural injection of blood, and in patients after operation, resemble the progressive lesion in appearance but not in behaviour. They added that if we accept a sufficiently broad definition of what constitutes pachymeningitis, we can find examples of it following various experimental procedures in animals, but there is no evidence that the lesion so produced is progressive.

Speaking of the fate of subdural hæmorrhages in human beings the authors said that Böckmann examined the duras of fifty-seven patients dying after various intracranial operations in which blood was presumably extravasated beneath the dura. The patients died at intervals of a few hours to two months after operation; in two cases the remains of a hæmatoma were found, but with little vascularity; he believed that a subdural hæmorrhage does not lead to pachymeningitis.

The authors repeated Böckmann's investigation by studying material from the surgical service of the Peter Bent Brigham Hospital. Specimens were taken from the preserved duras of eighteen patients who had died at various intervals after intracranial operations during the previous three years. The interval between operation and death varied from a few hours to three months. Their findings agreed with Böckmann's in that the subdural clots were always small, and never showed evidence of progressive or repeated hæmorrhage. On the other hand they did show the mesothelium lined spaces which, the authors said, apparently play an important part in the ætiology of recurrent bleeding, and which are rare in hæmatomas elsewhere in the body.

The Structure and Function of the Dura Mater in Relation to Subdural Hæmorrhage, Cysts, and False Membranes.

As the structure of the dura mater is of considerable importance in arriving at a proper understanding of subdural hæmorrhage, cysts, and false membranes, a few references to articles bearing on this subject will be given.

Weed (1917) said "this division of the cranial pachymeninx into two layers is quite arbitrary; there is nothing in the general histology of the

fibrous covering to suggest such a halving except its division about the sinuses and its spinal relationships." Referring to the subdural space Weed stated that Key and Retzius (1875) "demonstrated a typical mesothelial cell-lining on the inner surface of the dura, as shown by the method of silver reductions." Weed added: "The current impression that the subdural space is in many respects a serous cavity will probably finally have greatest support." Again Weed (1932), fifteen years later, said: "The inner surface of the dura mater is completely lined by flattened polygonal mesothelial cells with relatively large, pale oval nuclei."

Mallory (1920), as the result of his investigations, concluded that: "There is no dural endothelium; the inner surface of the dura is bare except for fibroblasts."

Trotter (1926) stated that breeches of the normal coverings of the nervous tissues allowing contact between the latter and other tissues of the body result of necessity in energetic local reactions. The obvious function of such reactive processes is to re-establish the normal discontinuity between neural and somatic tissues and to break the contact that has caused the disturbance.

This mechanism of a definitely physiological type, said Trotter, may well prove to be concerned with the very nature of the nervous system. If we are right in supposing that all neuro-somatic contacts are inadmissible and that the blood and blood-vessels belong to the somatic side of the frontier, the nutrition of so large a bulk of nervous tissue as the central nervous system must involve dispositions altogether unique in the body, and we should expect, in regarding the circulatory mechanisms of the part from this point of view, to meet with features of a very special kind. The dura and arachnoid are in some sense intermediate tissues, for they show a certain tolerance for both neural and non-neural contacts, the arachnoid having slightly greater affinities for the former, and the dura perhaps for the latter.

Woollard (1927) said Harvey and Burr (1926) were impressed by the behaviour of the meninges to injury. They remarked that when the dura is cut away without any injury to the underlying arachnoid, the gap is filled by organizing tissue without any reaction occurring in the underlying membrane. Mesothelium is formed over the inner face of the new tissue without any adhesion to the arachnoid. If, on the other hand, a flap of dura is turned back, the arachnoid injured and the flap replaced, reaction occurs in both structures and always results in the formation of adhesions. This difference appeared to them to indicate a difference in origin. The dura, being a skeletal membrane, they believed

to be of mesenchymatous origin, while the pia-arachnoid lining the nervous tissues, like the sheath of Schwann, with which it is homologous, they thought might be developed from the neural crest.

Leary and Edwards (1933) stated that the pia-arachnoid is the substitute for the lymphatic system of the brain, and forms a water bed for that organ. Among the membranous structures of the body it is *sui generis*. On the other hand, the dura is simply the lining of a bony cavity, a mechanical support for the brain and for the large sinuses needed to remove the venous blood. As a result of their investigations they considered that the subdural space does not correspond to the serous spaces; that the dura is not lined by mesothelium, but by fibroblastic tissue; that the arachnoid is covered by cells which do not appear to be mesothelial, which are probably of ectodermal origin and to which the arachnoid owes its impermeability.

Leary (1934) said: "The manifest differences in the two membranes lining the subdural space have suggested to me the concept that the skull, like other bones, enters into articulation. In this case the articulation is not with bone but with a compound organ, the brain with its covering pia-arachnoid. The relations of the two structures, skull lining and brain covering, are largely those of contiguity, the only continuity arising from nervous and vascular connections and minor supports for the falx. From this point of view the dura is the lining of an articulation and has the character of a simple fibroblastic tissue, which Maximow has shown to be the standard lining of the synovial spaces. This concept simplifies the approach to the study of subdural hemorrhages."

Maximow and Bloom (1943) make the following statements (p. 234): "The inner surface of the dura mater is smooth and covered with a layer of squamous mesothelial cells," also (p. 38), "Mesenchymal epithelium is the simple layer of squamous cells which lines the subdural and subarachnoid spaces, the perilymphatic spaces in the inner ear and the chambers of the eyeball. These elements seem to originate simply through flattening of common fibroblasts"; again, "The relations between mesenchymal epithelium and the mesothelium have not been sufficiently elucidated"; again "The cavities of joints are *not* lined by mesenchymal epithelium."

Le Gros Clark (1943) speaking of the dura mater of the brain said "This part of the dura mater is adherent to the inner surface of the cranial wall, and performs a double office. It serves as an internal periosteum for the bones which it lines, and it constitutes an envelope for the brain. Its inner surface is smooth and glistening and is covered with a layer of mesothelial cells." Later on he said, "the dura mater of the brain has

two layers intimately connected with each other, but yet capable of being demonstrated in most regions; and along certain lines they separate to enclose channels lined with endothelium. These channels are the venous blood sinuses, and they receive the blood from veins which come from various parts of the brain."

J. S. Robertson (1945), working in the Department of Pathology at the University of Sydney, used a silver reduction method on rabbit tissue and found that with peritoneum and pleura a continuous layer of lining cells could be clearly defined, because of the deposition of metallic silver on the so-called intercellular cement substance. Preparations of dura mater showed different appearances, and, though the outlines of some cells could be detected, a continuous layer of lining cells like those of serous membranes could not be demonstrated.

Phagocytic Properties of Cells Lining the Dura Mater.

In the present work evidence will be submitted that the lining cells of the dura mater act as macrophages and develop through fibroblasts into fibrous tissue. As it is held by many observers that the serosal cells and dural lining cells are akin, opinions as to the behaviour of serosal cells in regard to phagocytosis and to the formation of fibrous tissue are of importance.

Cunningham (1922*a*) said: "There is no evidence of transition between the normal serosal cells which have desquamated and the phagocytic monocytes of the exudate." "Desquamated serosal cells degenerate rapidly in the exudate." The serosal cells do not "proliferate to form new cells of the series"; "it seems assured that they represent a very highly specialized cell, acting as a lining cell for the serous cavities but capable of active secretory activity."

In regard to the relationship of the lining cell to the fibroblast Cunningham (1922*b*) came to the conclusion "that the mesothelial and fibroblastic elements are wholly specific."

Maximow and Bloom (1944) speaking of fibroblasts (p. 58) said there is "some indication that they become phagocytic on intense stimulation." Of desquamated mesothelial cells in serous exudates they said (p. 67): "In inflammation and tissue culture these cells develop into fibroblasts."

Muir (1941), referring to serosal cells, said that ordinarily they show no evidence of taking part in the formation of connective tissue, but there are indications of this in certain instances, there being all transitions between typical serosal cells on the surface and cells forming fibrils below. Such an appearance may be deceptive, but he believed that sometimes they may form connective tissue though usually there is no trace of this.

Muir said he formerly believed that the serosal cells were actively phagocytic towards damaged leucocytes, &c., but at the time of writing he was convinced, in agreement with most recent observers, that they have little or no phagocytic action.

Present Investigation.

Comparison of Serous Membranes with the Lining of the Dura Mater.

Portions of peritoneum, pericardium and dura mater from the body of a man 25 years of age were examined. The patient died of mitral stenosis with congestive cardiac failure. The peritoneum, pericardium, and dura mater appeared normal to the naked eye. There was increase of fluid in the pericardial cavity, but not in the peritoneal cavity nor in the subdural space.

The portions of tissue taken for histological study included parietal peritoneum, parietal pericardium and dura mater. Fig. 1 shows the appearance of the parietal peritoneum in a section cut at right angles to the surface. Resting on the fibrous connective tissue (in which there is an artificial cleft) a single layer of mesothelial cells is evident; their rounded or oval nuclei stand out clearly, but their cytoplasm is ill-defined.

Fig. 2 shows the appearance of the parietal pericardium in a section cut at right angles to the surface. Again we see dense fibrous tissue on which a clearly defined single layer of mesothelial cells is resting. The rounded or oval nuclei of the cells can be made out, but details of the cytoplasm are not distinct.

Fig. 4 shows the appearance of a section of the dura mater cut at right angles to the surface. In the upper part of the illustration the fibrous tissue appears to extend to the deep surface (on the right) without appreciable alteration. In the lower part there appear to be flat nuclei to indicate the lining of the dura mater. As a general rule the appearances of the deep surface of the dura mater, as seen in sections cut at right angles to the surface, are more like those in the upper half of fig. 4 than those in the lower half. Attempts were made to examine the lining cells of the dura mater in sections cut parallel with the surface; many of these sections showed the dura mater cut more horizontally than vertically, but really cut obliquely. Some portions of these sections showed appearances which seem to indicate that though the lining of the dura mater is different from the mesothelium of serous membranes—the lining cells and their nuclei are flatter and less clearly defined—they differ from the ordinary connective tissue cells of the fibrous tissue of the dura mater, and probably are to be regarded not as ordinary fibroblasts but as con-

nective tissue cells modified somewhat to meet the needs of their environment.

Fig. 5 shows a slightly oblique section of dura mater; on the right, which represents the deep surface, there is a zone of cells with nuclei that are rounded or oval in this plane of section, but not as elongated as those in the connective tissue to the left.

In fig. 6 we see another oblique section, and the difference between the lining cells on the right and those of the connective tissue on the left is again evident.

Similar appearances to those in figs. 1, 2, 4, 5 and 6 have been seen in specimens from other bodies, and the opinion has been formed that the dura mater is lined by a layer of modified connective tissue cells that differ from the mesothelial cells which line the serous cavities.

Up to the present, structural features have been considered, but functionally the lining cells of the dura mater seem different from those of a serous membrane.

In fig. 3 we see the early reaction of the pericardium in inflammation. To the left the fibrous tissue of visceral pericardium is evident, to the right there is fibrin with entangled leucocytes, and in the mid-line is a row of swollen mesothelial cells. Even when organization takes place these mesothelial cells do not seem to exercise phagocytic properties, or to form fibrous tissue.

The cells which line the dura mater, however, seem to be capable either of exercising phagocytic properties and ingesting blood pigment (*see* figs. 9 and 10) or of developing through fibroblasts (*see* figs. 17 and 22) into fibrous tissue (*see* figs. 29 and 35). Even if serosal cells have the capacity to act similarly on occasion, ordinarily they do not appear to do so.

It would seem therefore that regarded both from the point of view of structure and from the point of view of function the cells on the deep surface of the dura mater are different from the mesothelial cells that line serous sacs.

Case Reports.

The cases which have been studied in this investigation are arranged, according to outstanding gross characters, under the following headings.

I.—Those characterized by the presence of a subdural delicate false membrane with small extravasations of blood in the false membrane.

II.—Those in which a considerable amount of blood was present on the deep surface of the dura mater, hæmorrhage being the outstanding gross feature.

III.—A case of subdural hæmorrhage in which the naked-eye features, at first sight, suggested intra-dural hæmorrhage with splitting of the dura mater.

IV.—A case of subdural cyst.

V.—A case of subdural fibrous false membrane.

I.—Cases Characterized by the Presence of a Subdural Delicate False Membrane and Small Extravasations of Blood in the False Membrane.

Case 1.—The patient (S.H. 10,700), a man 43 years of age, was admitted to hospital approximately four months before death, having been struck on the right side of the forehead by a crane. There was a lacerated wound in the glabellar region. The patient was semiconscious and delirious on admission to hospital, but made favourable progress up to the time of his discharge four weeks after the injury. X-ray examination at this time revealed a fracture of the right maxilla, but no fracture of the skull.

One month before death the patient was readmitted to hospital with a carbuncle on the back of the neck. The carbuncle had commenced as a "pimple" nine days before readmission to hospital. The patient had had a similar carbuncle four years before.

On readmission physical examination showed all the systems to be clear; the knee-jerks were present. Five days after readmission the patient complained of a sore throat, the temperature rose to 103°F., and there was slight inflammation about the tonsils. Ten days after readmission the patient complained of dysphagia. Two days before death his arms were very weak, he complained of pains in the arms and legs, and he had to be catheterized.

Special tests.—Ten days after readmission the blood showed a neutrophile leucocytosis (19,000 leucocytes per c.mm. of which 90 per cent. were neutrophiles). The Wassermann test was negative. Clinically the condition was regarded as one of pachymeningitis of the cervical region of the spinal cord caused by direct extension of the infection from the carbuncle.

Post-mortem examination.—The body was that of a well-built man. There was the healing and granulating ulcer of a carbuncle at the back of the neck, in the mid-line. Both lungs showed hypostatic pneumonia. The heart and the abdominal organs showed no changes of special significance.

The spinal cord was damaged during removal; this was due to the fact that there was an area of softening in the cervical region of the cord at a level corresponding roughly with that of the carbuncle in the neck. The spinal cord broke at this level, and was removed in two pieces. The softening of the cord was probably related to the carbuncle in the neck.

Naked-eye examination of the false membrane.—On cutting through the dura mater a delicate membrane was found covering the greater part of the left cerebral hemisphere (fig. 7). The membrane was so delicate that it was difficult to avoid tearing it. For the most part it was from 1 mm. to 2 mm. thick, and resembled wet tissue paper. It was slightly yellowish or brownish in colour, except for those areas in the parietal and temporal regions where recent hæmorrhage had occurred. These hæmorrhagic areas consisted of fresh blood clot; it is hard to believe that they could have resulted directly from the injury four months before.

The hæmorrhagic membrane was not adherent to the arachnoid mater, but was very loosely adherent to the dura mater, from which, however, it was easily reflected, leaving a smooth surface very little different from that of normal dura mater.

Though the injury probably was responsible for starting the changes beneath the dura mater, the appearances found post mortem were not such as one would expect to find if injury had caused extravasation of blood which had undergone gradual and progressive organization.

Histology.—The structure of the delicate false membrane is to be seen in fig. 8. In contact with the under surface of the dura mater is a thin membrane which shows little structure; however a striking feature is the presence of collections of brown pigment (hæmosiderin). An earlier stage in the formation of the membrane is to be seen in fig. 9 and in fig. 10. In fig. 9 the earliest stage is recognizable; the membrane is only one cell thick. Nevertheless it can be recognized as abnormal by the presence of the hæmosiderin. The arrow points to an accumulation of hæmosiderin which masks the details of the cell which has ingested it. Immediately above and below this cell other lining cells can be seen which, except perhaps for slight swelling, might be regarded as normal. The small clefts which separate these lining cells from the fibrous tissue of the dura mater are artefacts, but they help to make the picture clearer. In fig. 10 a flake of the lining layer has been reflected and twisted so that for the most part the flat surface is to be seen. If the lining layer in fig. 10 is traced from the right bottom corner to the left, it is seen, near the attachment of the flake, to consist of cells which contain much hæmosiderin, but in the detached part there can be seen red blood cells, nuclei of lining cells, and small granules of hæmosiderin. In other parts of the membrane the lining cells have proliferated to form a membrane of appreciable thickness and in some situations the membrane is in two or more layers with much blood between the layers; this is the explanation of the presence of the two separate accumulations of extravasated blood which presents a striking feature in fig. 7.

Dr. Oliver Latham, who examined sections from the spinal cord, thought that the softening of the cord (which accounted for it breaking during removal) was toxic.

Case 2.—The patient (S.H. 4,698) was a man 34 years of age. When admitted to hospital his chief trouble was dimness of vision in both eyes, mainly the left. Eight weeks before admission he complained of gradually increasing pain in the right eye. Vision in the right eye gradually failed and disappeared completely, but steadily returned until he could see objects in a dim light. The left eye was normal until five days before admission when it became painful on movement and vision began to fail; vision in this eye gradually became worse, and eventually disappeared almost completely. He was troubled by headache, vomiting, and frequency of micturition He had had paralysis of the lower limbs (due to a "heavy strain") fourteen years before, and seven years later he had been operated on (gastro-enterostomy) for ruptured peptic ulcer. He was a heavy smoker, but did not take alcohol, had not worked with lead, and had not suffered from syphilis. The patient's legs were extremely wasted, his gait was somewhat ataxic and his knee-jerks were active. His temperature was not raised during his stay in hospital.

X-ray examination revealed nothing abnormal in sella turcica or sinuses; there was some pyorrhœal absorption of the gums, but no radiological evidence of septic foci.

The blood gave a negative result with the Wassermann test, and the blood-count showed 13,400 leucocytes per c.mm. (72 per cent. of them neutrophiles), but otherwise did not deviate much from normal. The cerebrospinal fluid was under slight pressure; it gave a negative reaction with the Wassermann test, contained no globulin, and in wet films only occasional red cells were seen. The urine contained pus, but no sugar and no lead.

Five weeks after admission to hospital both eyes showed optic atrophy. Ten weeks after admission the patient died.

Post-mortem examination.—The stomach and duodenum showed the result of posterior gastro-enterostomy. There was some thickening in the first part of the duodenum, probably indicating the site of a healed peptic ulcer. The urinary bladder was full of purulent urine.

The brain weighed 1,210 grm.; it was normal in appearance; no disease in the vessels or convolutions was found. On incising the brain no gross signs of disease were seen. On the deep surface of the dura mater, on the left side, was a false membrane in which there were extravasations of blood.

The spinal cord was not examined. The other organs presented no changes of special significance. The dura mater and the underlying membrane were submitted to detailed study.

Naked-eye description.—Fig. 11 shows portion of the affected dura mater. Loosely attached to the deep surface of the dura mater was a thin delicate membrane which was easily reflected, leaving a comparatively clean and smooth surface. In the upper part of fig. 11 the pale smooth surface of the dura mater can be seen after the false membrane has been peeled off and reflected downwards. Contrast the comparatively normal dural surface above with the lowest part of the illustration where the dura mater is still covered by the thin false membrane. This membrane had a somewhat rusty appearance in the fresh specimen, due to scattered red blood cells and granules of blood pigment (hæmosiderin). In the delicate membrane there are numerous small extravasations of blood, some of which have fused to form rather extensive hæmorrhagic areas with irregular outlines.

Histology.—The fibrous tissue of the dura mater is, in some places, somewhat fragmented, especially in the outer part. In the inner part, near the false membrane, the fibrous tissue is somewhat hyaline here and there, but, as the photomicrographs show, the structure of the dura mater deviates little from normal. In fig. 12 a fairly representative portion of the false membrane is to be seen. It is composed for the most part of elongated cells laid down parallel to one another and parallel to the inner surface of the dura mater. The cells nearest the free surface of the membrane, as is often the case in these membranes, form delicate layers of cells; these delicate layers tend to become separated from one another. Scattered among the elongated cells of the membrane red blood cells are to be seen; the red blood cells are especially clear near the centre of the illustration.

In fig. 13 the false membrane is rather more compact than in fig. 12.

Fig. 14 shows a portion of the membrane which looked hæmorrhagic to the naked eye. Red blood cells present a striking feature. Examination of the histological sections showed that blood pigment is also present, especially in the elongated cells of the membrane; these elongated cells are rather widely separated from one another, and do not form a relatively compact membrane such as is to be seen in fig. 13.

The exact site of the original extravasation of blood was not found. No red blood cells were seen on the free surface of the membrane, they were all incorporated in the membrane, which all appears to be new and not an altered part of the dura mater.

The appearances do not suggest splitting of the dura mater, the inner portion of the dura forming the false membrane.

It is possible that the extravasation took place in the deepest part of the dura and that the cells of this deepest part of the dura proliferated to form the false membrane; it seems, however, more likely that, as small amounts of blood spread on the inner surface of the dura mater, the dural lining cells proliferated and

enmeshed them, the red cells later undergoing disintegration and setting free blood pigment (hæmosiderin). The occasional red cells and granules of blood pigment in the membrane would account for its rusty appearance. Another point in favour of regarding the false membrane as all new, and not as portion of the dura mater which has become altered by hæmorrhage, is that the false membrane peels off the dura mater so easily, leaving a practically clean surface. Even if the false membrane is all new tissue it is difficult to explain why it is not more firmly united to the dura mater, but if the false membrane represented a portion of the dura mater itself the difficulty would be even greater.

Case 3.—The patient (S.H. 11,056) was a man 45 years of age, who, on admission to hospital, complained of weakness and shortness of breath, dry retching, anorexia and soreness of the tongue.

Examination of the blood showed red cells 2,090,000 per c.mm., hæmoglobin 38 per cent., colour-index 0·95, anisocytosis and poikilocytosis; there were 4,500 leucocytes per c.mm. of which a few were neutrophiles and lymphocytes, but large cells of primitive type predominated.

The Van den Bergh test gave an indirect positive result; there was no occult blood in the stools, and there was total achlorhydria.

The provisional diagnosis was aleukæmic leukæmia, but the patient was given the treatment for Addisonian anæmia, and this resulted in some increase of red blood cells and of hæmoglobin. However, during four months the colour-index remained high (0·9, 1, 1·2), leucopenia persisted (3,520, 3,280, 3,840), and primitive cells became still more prominent. The patient lived for eight months after admission to hospital.

Post-mortem examination.—This revealed extensive infiltration of all the organs which were examined by primitive leucocytes and cells of the granular series.

Naked-eye description of the subdural lesion.—The changes are well shown in figs. 15 and 16. Covering the anterior and middle part of the deep surface of the dura mater on the right side, from the mid-line to a distance of 7 cm. where the dura had been cut in an antero-posterior direction, was a delicate rusty membrane thinner than tissue paper. On the falx, from one end to the other, there was a faint indication of a similar membrane, and on the posterior third of the dura mater on the right side a slight suspicion of yellowish coloration was also evident. Throughout the membrane proper there were small hæmorrhages varying from microscopic dimensions up to 0·5 cm. in diameter and 1 mm. in thickness. Many of the hæmorrhagic areas fused laterally to form relatively extensive extravasations of blood. The membrane was readily reflected from the dura mater leaving a few faint red marks where slender vascular connections existed between the dura mater and the false membrane. Around some of the extravasations of blood, slender blood-vessels could be seen to radiate (fig. 16). These vessels were very delicate but they could be recognized with the naked eye. Presumably they were branches of the delicate vessels which passed from the dura mater into the false membrane, vessels which easily broke asunder when the false membrane was reflected from the dura mater. The left side of the falx cerebri showed the beginning of a faintly brown membrane, and a suspicion of yellowish coloration, but no definite membrane, could be seen spreading widely on the deep surface of the dura mater on the left side. The main blood-vessels of the dura mater looked normal on both left and right sides.

Histology.—Fig. 17 shows that the membrane in this case closely resembles that in Case 2 (*see* fig. 12). There is clear-cut demarcation between the fibrous dura mater and the false membrane, which in its deeper part is composed chiefly of red

blood cells and primitive leucocytes, and, in its superficial part, of proliferated lining cells some of which appear to have cytoplasmic processes, an appearance which is interpreted as an indication of a formative tendency of lining cells in their development towards fibrous connective tissue.

Fig. 18 shows the superficial part of the false membrane cut horizontally. The nuclei of the proliferated lining cells present a somewhat different appearance when cut horizontally, and their cytoplasmic processes present a striking feature, forming a fine felted network; scattered red cells are also to be seen, especially on the extreme right of the illustration.

Fig. 19 shows the appearance of one of the hæmorrhagic areas. It somewhat resembles the hæmorrhagic area shown in fig. 14 (Case 2). Red blood cells and especially primitive leucocytes dominate the picture, but proliferated lining cells are also present, and no doubt form the framework of this portion of the membrane.

Hæmorrhagic lesions like those on the deep surface of the dura mater (fig. 15) were also present on the pleura. The impression gained by naked-eye investigation was that the lesions of the pleura did not peel off as readily as those of the dura mater. With this in mind, sections of one of the pleural lesions were cut, to see if any differences could be recognized. Without wishing to attach too much importance to observations made on one case, the opinion was formed that, whereas in the subdural lesion there was a clear-cut line of demarcation between hæmorrhagic lesion and dura mater proper, permitting of the stripping away of the hæmorrhagic membrane to leave a comparatively normal and intact dura mater, a different state of affairs obtained with the pleura.

Fig. 20 shows a lesion of the parietal pleura. The connective tissue of the pleura can be seen as an ill-defined narrow zone passing transversely across the upper part of the illustration. The uppermost part of the illustration shows a few rounded spaces representing extrapleural adipose tissue, but this part of the section is heavily infiltrated by primitive leucocytes. Below the level of the pleural connective tissue there is tissue which projected into the pleural cavity and which is composed largely of primitive leucocytes but also, to a considerable extent, of connective tissue cells and young blood-vessels.

Clearly this lesion could not be peeled off the pleura, and the involvement of the pleural and extrapleural tissues is in marked contrast to what is to be seen in the dura mater (fig. 19), where there is such a clear-cut line of demarcation between subdural membrane and comparatively unaffected dura mater.

II.—Cases in which a Considerable Amount of Blood was Present on the Deep Surface of the Dura Mater, Hæmorrhage being the Outstanding Gross Feature.

Case 4.—The patient (S.H. 7,828), a man 54 years of age, was admitted to hospital, with a history that he had been unconscious for four days during which time he had had several fits. When examined he was found to be semiconscious; he could give no history of his illness though he could talk nonsense. Nothing of special significance was found in the respiratory or circulatory systems; he had incontinence of urine.

The pupils were contracted but reacted to light; epigastric reflexes were absent, knee-jerks were active and patellar jerks were present. There was paresis of the right upper and lower extremities.

The blood and cerebrospinal fluid gave negative results with the Wassermann test. Blood urea was 61 mg. per 100 c.c. and blood creatinine 4 mg. per 100 c.c.

The patient had two epileptiform fits while in hospital and he died twelve days after admission, having been unconscious off and on for sixteen days.

Post-mortem examination.—There was no free fluid in the pleural cavities. The *right lung* weighed 680 grm.; the lower lobe was partly consolidated and the remainder of the lung was congested. The bronchi of the lower lobe contained pus. The *left lung* weighed 425 grm.; it was congested and œdematous but there was no pus in the bronchi.

The *heart* weighed 425 grm.; the left ventricle was slightly hypertrophied and there was slight fibrosis of the muscle. Valves and aorta were normal.

Each kidney weighed 85 grm. and had an adherent capsule which left a granular surface when removed from the kidney. The cortex of the kidney was diminished and the pelvic adipose tissue was increased in amount. Microscopically there was evidence of nephrosclerosis.

All of the other organs were normal except the brain.

Naked-eye description of the brain and its membranes.—The brain weighed 1,190 grm. There was an accumulation of blood, measuring approximately 2·5 cm. in all diameters in the anterior part of the left frontal lobe. Where this hæmorrhage extended (by rupture) to the surface of the brain the opening was less than 1 cm. in diameter. The opinion formed at the post-mortem examination was that hæmorrhage had occurred in the substance of the left frontal lobe (not a cortical hæmorrhage), and that the blood had ploughed through the healthy cerebral tissue to the surface of the brain (anterior pole of the left frontal lobe), and had then spread beneath the dura mater. A large amount of blood clot was adherent to the deep surface of the dura mater where it was attached to the vertex of the skull and also where it was attached to the base of the skull, but, though the pia-arachnoid was blood-stained, no gross blood clot was present in its meshes. The blood in the substance of the brain was dark red in colour and was clotted. It is practically certain that this hæmorrhage occurred in the brain tissue and did not extend into the brain from the membranes. It is possible that the subdural hæmorrhage was independent of the cerebral hæmorrhage, but this seems very unlikely.

The reason why a suggestion is made that the subdural hæmorrhage and the hæmorrhage in the substance of the brain may have been independent in Case 4 is that such an association was met with in another case (not included in this series). In that case the patient gave a history of injury to the head a month before death and post-mortem examination revealed a subdural fibrocellular and hæmorrhagic false membrane as well as numerous small hæmorrhages in the substance of the pons; the largest of these pontine hæmorrhages was little more than a centimetre in diameter. In that case, however, there was no close anatomical relationship between the hæmorrhages in the substance of the brain and the subdural false membrane, whereas in Case 4 there appeared to be direct communication between the hæmorrhage in the substance of the brain and the hæmorrhage in the subdural space.

Histology.—The microscopic appearance of the dura mater is shown in fig. 21. The dura mater itself shows no special changes. The fibrous tissue of the dura mater is perhaps a little more homogeneous than usual, and in places it seems to be a little thicker than normal.

Adherent to the inner surface of the dura mater is a membrane composed mostly of cells which look like fibroblasts. These cells run irregularly. Blood spaces are numerous especially in the portion of membrane near the dura mater. Speaking generally the membrane is not as dense near the dura mater as in its deeper part. Phagocytes, many containing blood pigment, and leucocytes, many with polymorphous nuclei, are present in the membrane. Much blood clot is present in the section, but this is not included in the illustration.

In parts of the section the false membrane can be seen to blend with the underlying blood clot. The blood clot contains very large numbers of polymorphonuclear

cells. The strand shown on the lowest part of fig. 21 communicates with a large mass of loosely attached blood clot.

Case 5.—There is some doubt concerning the clinical history of this case (S.H. 11,055), but there is no doubt that it comes into group II which includes cases where hæmorrhage was the gross outstanding feature. There was a large amount of blood in the subdural space.

Histology.—The membrane has a structure rather different from that of the membranes in earlier cases. In parts where the accumulation of blood is not great (fig. 22) it seems to be composed of fibroblastic connective tissue with dilated vessels, some of which have ruptured. In other situations, where blood is abundant, similar fibroblastic cells can be seen in thin layers separated from each other by appreciable quantities of blood.

Case 6.—The patient (S.H. 9,903) was a man 54 years of age. Five weeks before death he fell while handling a horse, and he struck the back of his head. There were no immediate symptoms, but that night he suffered from a headache, and this persisted night and day for three weeks. The headache then became worse, and the patient became comatose.

Lumbar puncture was performed, and the cerebrospinal fluid was found to be under increased pressure but quite clear; no micro-organisms were found in it, and there was no increase in cells. The Wassermann test with the cerebrospinal fluid showed an incomplete positive reaction.

After repeated lumbar punctures the patient became sufficiently conscious to recognize his people. Four days later he again became comatose and he died after five weeks' illness.

Naked-eye description of the brain and its membranes.—Post-mortem examination revealed firm blood clot attached to the deep surface of the dura mater in the left occipital region. The underlying brain tissue did not appear to be damaged. The deep surface of the dura mater on the right side showed generalized congestion. The cortical vessels were very dilated, but otherwise no naked-eye changes of special significance were seen in the brain.

Histology.—The membrane is similar to that in Case 4 (*see* fig. 21) except that blood channels and extravasations of blood into the membrane are more conspicuous. The microscopical characters of the membrane are shown in fig. 23. The left side of the illustration represents the surface of the membrane which was loosely attached to the deep surface of the dura mater.

Large vascular channels are conspicuous in this situation; but they are not limited to this site, as quite large and conspicuous blood channels are to be seen extending through the membrane. In addition to the clearly defined vascular channels in the membrane, extravasations of blood of various sizes are to be seen scattered widely through its substance.

The impression gained is that some of the thinner walled vascular channels have ruptured and thus led to the extravasations of blood (*see* fig. 24).

III.—A Case of Subdural Hæmorrhage in which the Naked-eye Features, at First Sight, Suggested Intra-dural Hæmorrhage with Splitting of the Dura Mater.

Case 7.—The patient (S.U. 7,268), a woman 65 years of age, was admitted to hospital in an unconscious state; it was said that she had been unconscious for two days. The right side of the face, the right arm, and the right leg were paralysed.

Naked-eye description of the intracranial lesion.—The description by the patho-

logist who carried out the post-mortem examination was to the following effect. The dura mater was densely adherent to the calvarium. A large recent hæmorrhage was present in the dura mater attached to the dome of the skull on the left side. The blood had forced its way into the dura mater, and had divided it into two layers. The blood clot extended from the occipital protuberance forwards for a distance of 18 cm. and from the mid-line laterally for a distance of 9 cm.

Fig. 25 is a drawing which gives a general impression of the lesion. The gross accumulation of blood does not end abruptly at its margin but merges insensibly in a delicate membrane like those described in Cases 1 and 2. In the lowest part of the illustration, where an incision through the lesion is represented, the blood is shown to be situated between two layers of false membrane, the outer layer being in contact with the dura mater.

Histology.—Fig. 26 shows the margin of the large space filled with blood clot. The blood was present in what was practically an extensive flattened sac. In this illustration much of the blood has fallen away in preparing the section; a considerable amount, however, is still present.

The outer layer of tissue is composed of two parts, an external dense fibrous part, the dura mater, and an internal more cellular part which is essentially the same as the inner layer of tissue which bounds the blot clot on its deep aspect, and with which it fuses to form a compact more or less cellular membrane. This compact membrane, in the lower part of fig. 26, somewhat resembles that shown in fig. 13, Case 2, except that it is thicker and somewhat denser; however, it is not as dense and fibrous as the membrane shown in fig. 35, Case 9.

IV.—A Case of Subdural Cyst.

Case 8.—The patient (S.H. 7,722), a married woman 43 years of age, was admitted to hospital in a stuporous condition. She had been in this state for two weeks. She was first paralysed on the right side and later on the left also. She was unable to speak, and no further history could be obtained. Physical examination revealed nothing abnormal except in the nervous system. The pupils were equal and fixed, and there were slight oscillatory movements of the eyeballs. The right naso-labial fold was smoothed out, and there was paralysis of the limbs on both sides of the body. The wrist and elbow jerks were both present, the right being greater than normal; the knee-jerks were both present, the right being more marked than the left. There was slight patellar clonus on the right side, but no ankle clonus. The plantar reflex was extensor on both sides.

Lumbar puncture was performed and about 30 c.c. of clear fluid were withdrawn. The fluid was under pressure and it contained blood.

On admission to hospital the patient's temperature was 100°F.; it gradually rose to 105·8°F. just before death, which occurred two days after admission to hospital; that was sixteen days after the onset of the illness.

Post-mortem examination.—This revealed bronchopneumonia and pleurisy but otherwise nothing of significance in any organ except the brain and its membranes. The spinal cord was not examined.

Naked-eye description of the changes in the brain and its membranes.—Dura mater and cyst: On removing the calvarium, about 8 oz. of fluid escaped from a cyst situated over the left cerebral hemisphere. In appearance this fluid resembled cerebrospinal fluid coloured by dark blood. In this situation the dura mater was adherent to the calvarium. The cyst (fig. 27) was situated between the dura mater and the arachnoid, being loosely adherent to the under surface of the dura mater,

but not adherent to the arachnoid. The cyst had apparently been tensely filled with fluid which was brownish in colour. The wall of the cyst was thinner where in contact with the arachnoid than where in contact with the dura mater. The cyst extended from the anterior pole backwards over the upper part of the frontal lobe and of the parietal lobe for a distance of 13·5 cm.

In fig. 27 the relation of the cyst to the dura mater is not very clear except posteriorly where the under surface of the dura mater, which has become somewhat plicated during fixation, is seen to be in contact with the cyst wall.

Two holes are present in the cyst wall, a large one near the anterior end (this hole was made to pack the cyst with cotton-wool prior to fixation), and a smaller one (made accidentally) just posterior to the middle of the cyst. The smaller hole is in the portion of the cyst wall which was in contact with the dura mater; this portion, though thicker than that which was in contact with the arachnoid, contained less mature connective tissue (*see* figs. 28 and 29).

On the outer surface of the cyst wall (as shown in fig. 27) an indefinite ridge, running lengthways, indicates the margin between the portion of the wall above, which was in contact with the dura mater, and the portion of wall below, which was in contact with the arachnoid.

In some situations, where the relations of the cyst to the dura mater had not been disturbed, a thin delicate membrane could be seen extending beyond the margin of the cyst on to the deep surface of the dura mater, the appearances resembling those presented by Case 7 (figs. 25 and 26).

Brain.—The cerebellum, pons, medulla, and right cerebral hemisphere were apparently normal, and the vessels at the base of the brain seemed normal. The left frontal and parietal lobes, on which the cyst pressed, were small and flattened, and an extensive area of superficial necrosis was evident in this region, particularly when the brain was cut horizontally. It seems probable that the damage to the cerebral tissue was due to pressure by the subdural cyst.

Histology.—Dura mater and cyst: Fig. 28 shows the part of the wall of the cyst which was loosely adherent to the deep surface of the dura mater. The line of contact with the dura mater is shown at the upper limit of the illustration. This portion of the cyst wall is thicker than the portion resting on the arachnoid (fig. 29).

In the upper part of fig. 28 (the part nearest to the dura mater) spaces are conspicuous. These are thought to be blood channels. The tissue separating these spaces is thought to be composed of formative connective tissue cells not so far advanced in development as the connective tissue in the part of the cyst wall which rested on the arachnoid (fig. 29). In the lower part of fig. 28 the tissue is very cellular, many of these cells being leucocytes, the great majority lymphocytes; even in this lower part, however, connective tissue cells account for most of the tissue, the blood-vessels being much less conspicuous than in the upper part of the figure.

Fig. 29 shows that part of the cyst wall which was resting on the arachnoid; the more cellular zone to the right was resting on the arachnoid, the older and fibrous zone was nearer the lumen of the cyst. A small amount of blood in the lumen of the cyst is still adherent to the inner surface of the wall. The wavy fibrous tissue is much more mature than the connective tissue shown in fig. 28, and it showed the staining reactions for collagen. It will be noted that there are no blood-vessels in this portion of the wall which was resting on the arachnoid. Blood-vessels were continued from the outer portion of the wall of the cyst (loosely attached to the dura mater) across the margin of the cyst, and continued for some distance into the inner portion of the wall of the cyst (resting on the arachnoid), but then they ended, leaving a considerable area of the inner wall of the cyst avascular (fig. 29).

Near the junction between inner and outer portions of the wall of the cyst, that

is near the cyst margin, unusual vascular arrangements were present. Two of these are shown in figs. 30 and 31. Fig. 30 shows portion of the outer wall of the cyst near its junction with the inner wall (at the margin of the cyst). The dura mater is situated above the uppermost portion represented in fig. 30, and the more cellular inflammatory part of the outer wall (that is near the lumen of the cyst) is deeper than the part illustrated in fig. 30. In other words if the portion of the outer wall illustrated in fig. 28 is followed laterally towards the junction of outer and inner walls of the cyst, then, near the junction, the empty vascular spaces are very conspicuous near the dura mater, and the wall is too thick for the more cellular inflammatory tissue near the lumen to be included in this illustration (fig. 30).

The black particles scattered about in portions of the tissue shown in fig. 30 consist of old blood pigment, and are essentially the same as those in the fibrous membrane of Case 9 (*see* fig. 35).

Not all parts of this zone near the junction of inner and outer portions of the cyst wall showed empty vessels, indeed many parts were very congested; this is well seen in fig. 31, where the dilated vessels filled with blood present a striking appearance. The inner wall of the cyst for the most part was avascular, but vessels with dural connections passed from the outer wall into the peripheral part of the inner wall and these vessels were filled with blood.

Brain.—The histological structure of portion of the damaged cerebral tissue underlying the cyst is to be seen in fig. 32. Pia-arachnoid is included above; dilated and engorged vessels are conspicuous; the pale bands of tissue distributed throughout the field represent nervous tissue; the spaces contain degenerate fragments. In fig. 33 the effects of damage to the nervous tissue are seen to be extreme. No nervous structures are recognizable; lipoid-laden histiocytes dominate the picture on the left; large cholesterol clefts and cellular debris are conspicuous on the right.

V.—A Case of Subdural Fibrous False Membrane.

Case 9.—All that is known of this case is that the brain came from the body of a patient in a mental hospital.

Naked-eye description of the brain and its membranes.—Fig. 34 is a drawing of the gross specimen. The pia-arachnoid has been removed from the anterior half of the right cerebral hemisphere, but left intact over the posterior half. The dura mater which has been turned upwards showed no appreciable deviation from normal. Deep to the dura mater is a fibrous membrane. In the fixed state it is whitish in colour with a tinge of reddish-brown. It extends widely over the upper part of the right cerebral hemisphere. The membrane is loosely attached to the dura mater posteriorly, but for the greater part of its extent it is quite separate from the dura mater (to which no doubt it was originally loosely attached). This fibrous false membrane varies in thickness; posteriorly it is of approximately the same thickness as the dura mater but anteriorly it is much thicker than the dura mater. The membrane is nowhere attached to the arachnoid, but there are two small rough areas on its deep surface anteriorly.

Histology.—Fig. 35 shows the dura mater and false membrane where they are in opposition. The dura mater shows no special abnormality. The false membrane is composed of fibro-cellular connective tissue in which are irregularly scattered black masses especially in the part of the membrane near the dura mater. In the histological preparation these masses were found to be deposits of old brown-coloured blood pigment. Where the membrane is much thicker than it is in fig. 35 the connective tissue is more degenerate, and broken down red blood cells and blood pigment are to be seen widely scattered throughout the false membrane.

General Commentary.

In considering the cases included in this contribution and those described by earlier investigators, various questions suggest themselves for discussion.

(1) What is the nature of the lining of the dura mater?

(2) Are the lesions under consideration primarily inflammatory or primarily hæmorrhagic?

(3) What are the structural appearances of the lesions? (*a*) When the amount of blood in the subdural space is relatively small. (*b*) When there is a relatively large amount of blood in the subdural space.

(4) Should a distinction be drawn between massive subdural hæmorrhages and those that are petechial or conglomerate petechial?

(5) What are the causes of subdural hæmorrhage?

(6) Can any satisfactory explanation be given for the special features that are distinctive of these lesions?

(1) What is the Nature of the Lining of the Dura Mater?

The long-established, and still widely held, view that the dura mater is lined by a single layer of mesothelial cells like those lining a serous sac has been opposed by Mallory (1920) and by Leary and Edwards (1933). These investigators consider that the dura mater is lined by fibroblastic tissue.

In the present work the histological preparations show a striking difference between the lining of serous sacs (pericardium and peritoneum) on the one hand and the lining of the dura mater on the other (*see* figs 1 to 6 inclusive). There appears to be a specialized lining of the dura mater by modified connective tissue cells, these cells differing from ordinary fibroblasts, as is to be seen in figs. 5 and 6.

The mesothelial cells which line serous sacs are regarded by most authorities as being non-phagocytic and (in general) as being incapable of developing through fibroblasts to fibrous tissue. From evidence submitted in the present contribution, however, it would seem that the cells which line the dura mater are phagocytic, and are capable of ingesting blood pigment in considerable amount (*see* figs. 8 to 10 inclusive). It would also seem that these lining cells are capable of developing through fibroblasts (figs. 17 and 22) into fibrous tissue (figs. 29 and 35). The cells that line the dura mater differ from the general connective tissue of the dura mater (*see* figs. 5 and 6).

To sum up, the dura mater is lined by modified connective tissue cells which differ from the mesothelial cells that line serous sacs, and which

are capable of exercising phagocytic properties or of developing into fibrocellular connective tissue.

(2) Are the Lesions Under Consideration Primarily Inflammatory or Primarily Hæmorrhagic?

Virchow (1857, 1863) stressed inflammation as a likely cause, and attached importance to the presence of fibrin in subdural false membranes. In some cases in the present series fibrin was demonstrated in the false membrane, but this fibrin was considered to have come from extravasated blood.

Many writers have described subdural hæmorrhage as occurring in patients suffering from some infective condition, occasionally infection related to the central nervous system. In one patient in the present series (Case 1) there was a carbuncle in the neck, and toxic (?) changes in spinal cord.

From a study of the cases included in this series it would seem (*a*) that infection is rarely present and is not an essential feature, (*b*) that subdural hæmorrhage, in small scattered foci, or as a single large extravasation, is always present from the outset, and is the essential condition, (*c*) that the name pachymeningitis hæmorrhagica, in the sense that Virchow used it, should be discarded.

(3) What are the Structural Appearances of the Lesions?

(*a*) *When the amount of blood in the subdural space is relatively small.*—A small amount of blood may be extravasated into the deepest portion of the dura mater, but for all practical purposes the process begins with an oozing of blood, which finds its way on to the free surface of the dura mater (maybe in several situations), and then spreads over the deep surface of the dura mater for varying distances.

The reaction at the outset takes the form of proliferation of the special modified connective tissue cells which line the dura mater. At this stage red cells can be seen mixed up with the lining cells (*see* figs. 10 and 12). Many of the red cells soon break down and granules of hæmosiderin become ingested by the lining cells (*see* figs. 8 to 10 inclusive). The proliferation of the lining cells may be fairly considerable even though the number of extravasated red cells is small (*see* figs. 12 and 13). The changes described so far result in the formation of a delicate thin membrane of a faint rusty colour which extends widely on the deep surface of the dura mater, from which it is easily reflected leaving a smooth shiny surface. In certain situations, however, where definite hæmorrhages can be recognized with the naked eye, blood dominates the histological picture

(*see* fig. 14), red blood cells are dotted about in the membrane, and some of the proliferated lining cells have ingested much hæmosiderin. Up to this stage the outstanding changes, so far as the lining cells are concerned, are that they have proliferated and that many of them have acted as macrophages and ingested hæmosiderin.

The next change that becomes evident is that many of the lining cells develop into fibroblasts. These vary in their appearance in different cases and at different stages. Occasionally the cytoplasm of these cells may have many delicate branches (*see* figs. 17 and 18), more commonly they are seen as fairly compactly arranged young connective tissue cells presenting no features of special significance (*see* fig. 22). Eventually the fibroblasts develop into fibrous tissue (*see* figs. 29 and 35).

At the early stage of the differentiation of lining cells into fibroblasts, young vessels pass from the deep surface of the dura mater into the new membrane, and occasionally they can be seen radiating out from their point of entry into a hæmorrhagic area in the membrane and spreading in the surrounding delicate rusty and relatively non-hæmorrhagic part of the membrane (*see* fig. 16). These vessels that pass from the dura mater into the membrane provide practically the sole link between the dura mater and the false membrane, whether this membrane be delicate and friable, or relatively dense and fibrous. The two developmental tendencies of the cells that line the dura mater, namely into macrophages on the one hand and through fibroblasts into fibrous tissue on the other, overlap, and the two processes can be seen in operation at one and the same time.

The vessels in the substance of the false membrane sometimes have very thin walls and the appearances suggest that rupture of some of these vessels accounts for extravasations in the substance of the membrane. In this way fresh hæmorrhages (not from the site of the original hæmorrhage) could occur from time to time, long after the occurrence of the hæmorrhage which first accounted for the formation of the membrane. Thus the condition could be progressive.

Subdural false membranes are not attached to the arachnoid at all, and they may be stripped from the deep surface of the dura mater with great ease, the scanty, small, relatively delicate vessels passing from the dura mater into the membrane being broken in the process.

This lack of union between dura mater and false membrane is the most distinctive feature of the condition, and is not found in similar circumstances in any other part of the body such as serous cavities. This unique form of reaction may be linked up with the neuro-insulation theory of Trotter (1926).

(*b*) When there is a relatively large amount of blood in the subdural space the membrane which forms is essentially of the same nature as that which results from extravasations of small quantities of blood. The membrane, however, is usually in two parts which form an outer thicker wall and an inner thinner wall. The outer wall is loosely adherent to the dura mater from which it can easily be separated.

The inner wall is formed as a result of cells which line the dura mater growing in from the margin over the deep surface of the extravasated blood while it is still a firm clot. When a large amount of fluid blood or of blood-stained fluid is contained in a sac the inner wall resting on the arachnoid tends to be thinner and less vascular than the outer. Vessels pass from the outer wall a short distance across the margin of the cyst into the inner wall but do not reach the central area, much of the inner wall may thus be avascular. There is characteristically no link whatever (vascular or otherwise) between the arachnoid and the cyst. In other words the arachnoid plays no part in the formation of subdural false membranes or cysts. At the margin of the cyst the inner and outer walls of the cyst merge and extend peripherally as a single layer of false membrane essentially the same as that met with when there is no cyst. No example of splitting of the dura mater was met with in the present series. On one occasion (Case 7) the gross features suggested this, but histologically it was found that the blood was situated, not in the substance of the dura mater, but between two layers of false membrane which fused laterally to form a single layer (*see* fig. 26). In similar fashion the subdural cyst (Case 8), at its margin, merged in a single layer of false membrane corresponding to the false membranes unassociated with cyst formation. The fibrous membrane met with on one occasion (Case 9) showed none of the early stages of membrane formation as revealed by Cases 1 and 2 for example. It showed only the end-result of the process, rather old fibrous connective tissue with abundant scattered small clumps of hæmosiderin; there was no indication that cyst formation had been present at an earlier stage.

The retrograde changes of the cerebral tissue immediately beneath the cyst in Case 8 were regarded as secondary to pressure by the cyst. Probably the explanation of subdural cyst formation given by Zollinger and Gross (1934) is correct, namely that the cyst is due to the products of disintegrated blood leading to the passage of fluid, most likely from blood plasma (and not cerebrospinal fluid as suggested by Gardner, 1932) through the wall of the cyst, which acts as a semipermeable membrane. Late onset of symptoms may be accounted for by the slow formation of a cyst

as indicated above or, where there is no cyst, by hæmorrhage into a false membrane from thin-walled vessels in the membrane. These hæmorrhages into the membrane may occur on several occasions subsequent to the occurrence of the initial hæmorrhage which led to the formation of the membrane in the first instance; these repeated hæmorrhages may account for the intermittent character of the clinical manifestations which are a striking feature in some cases.

(4) Should a Distinction be Drawn Between Massive Subdural Hæmorrhages and those that are Petechial or Conglomerate Petechial?

A study of the cases recorded in the present contribution shows that, so far as the reaction to the presence of blood in the subdural space is concerned, there is no essential difference whether the amount of blood be small or large. In Case 1 there were separate extravasations of blood yet none of the terms minor petechial, conglomerate petechial, or massive is strictly applicable. Case 2 might be called conglomerate petechial, so might Case 3 where the extravasated blood was leukæmic. Cases 4, 5, 6 and 7 showed massive accumulations of blood. In Case 8 there was a large cyst and in Case 9 an old fibrous membrane with much hæmosiderin in it. The reaction was essentially the same in all cases.

In Case 7 there was a flattened cavity containing blood and in Case 8 a cyst containing blood-stained fluid, but when the inner and outer walls in these two cases were traced laterally, until they fused and blended, they continued peripherally for an appreciable distance as a membrane essentially the same as that present in the inner and outer walls (*see* fig. 26). Leary over-simplified the problem when he said "minor hæmorrhages with relation to the dura or the subdural space have no clinical significance, do not constitute hæmatomas and can be excluded."

The present study is concerned with the understanding of the disease as a whole, and is not limited to massive hæmorrhage or hæmorrhage caused by trauma. Subdural hæmorrhage following trauma is not always massive. For example in Case 1 of the present series there was a history of trauma, and there were associated clinical manifestations, yet the hæmorrhage was not a single massive one, indeed portions of the hæmorrhagic membrane were extremely delicate (*see* figs. 8 to 10).

In Case 2 of the present series, though there was no history of trauma and the subdural hæmorrhage was not massive, there were clinical manifestations reasonably regarded as related to the subdural hæmorrhage, though this relationship may have been an indirect one.

To sum up, it is thought that, so far as the unique reaction to extravasated blood in the subdural space is concerned, no essential distinction can be drawn between (*a*) extravasations that are massive and those that are petechial or conglomerate petechial; (*b*) extravasations that cause clinical manifestations and those that do not; (*c*) extravasations that follow trauma and those that occur apart from trauma.

(5) What are the Causes of Subdural Hæmorrhage?

The abstracts included in the historical sketch show that the possible causes of subdural hæmorrhage are many and varied. It may be found at any age and even in the fœtus (Pigeaud, 1928). Virchow (1857 and 1863) recognized that it might arise from trauma, or from hæmorrhagic, valvular or vascular disease. Sutherland (1894) found subdural hæmorrhage associated with scurvy in two infants.

Trotter (1914-15) thought the hæmorrhages entirely and solely of traumatic origin in his cases. Putnam (1925) distinguished between the membrane of traumatic hæmatoma which, on the dural side of the membrane, he said, contained mesothelium lined spaces, and that of the commonly described pachymeningitis hæmorrhagica interna in which, he said, no mesothelium lined spaces are seen. This distinction drawn by Putnam could not be made in the present series of cases. Cushing (1925) accepted the opinion that the majority of cases of subdural hæmatoma follow on trauma.

In the cases described by Russell and Cairns (1934) hæmorrhage was due to rupture of vessels following mechanical interference with the circulation by permeation of veins and capillaries with growth. Subdural hæmorrhage in children has been widely attributed to trauma especially birth trauma (Chase, 1930) but various infections such as syphilis (Debré and Semelaigne, 1926) have been thought to play a part as also have rickets (Sherwood, 1930) and scurvy (Sutherland, 1894). Subdural hæmorrhage in the fœtus has been attributed to syphilis (Pigeaud, 1928).

Subdural hæmorrhage has been found in association with maldevelopment of the brain (Sutherland and Paterson, 1913). It is possible that in such instances the vessels may be prone to rupture because of faulty development.

In the present series of cases a history of trauma was given in some but not in others. One case was definitely associated with leukæmia. The only points that all the cases appear to have in common are (*a*) that blood (normal or abnormal) was present in the subdural space, and, it is suggested, (b) the barrier between neural and non-neural tissues was maintained (this seems doubtful in Case 4).

(6) Can any Satisfactory Explanation be given for the Special Features that are Distinctive of these Lesions?

The distinctive features are:—

(1) That the extravasated blood leads to the formation of a hæmorrhagic false membrane (or occasionally a cyst) very loosely attached to the dura mater (mainly by delicate blood-vessels), from which it can be easily reflected leaving a smooth surface.

(2) That the false membrane (or cyst) is quite free.from the arachnoid which takes no part in its formation.

(3) That the condition, instead of ending in the formation of adhesions or a scar, tends to persist and progress.

In fibrinous pericarditis the inflammatory tissue, from an early stage of organization of the fibrinous exudate, is bound to the surface of the heart. If, instead of fibrinous exudates, blood clot on a serous surface is being organized, I believe that the same firm union takes place and that, when both parietal and visceral layers are involved, adhesions form.

In tertiary syphilis involving the membranes of the brain, adhesions form between the brain and its membranes and sections cut through the affected part show continuity of tissue through the dura mater, the intervening adhesions, and the cerebral substance.

Leary (1939) considered that the persistence which is the outstanding characteristic of subdural hæmorrhages as compared with hæmorrhages elsewhere in the body arises from the fact that the burden of organizing and removing the clot is thrown on a poorly vascularized dense connective tissue membrane that is in contact with only one surface of the clot and has difficulty in carrying out its assignment; however even when the amount of extravasated blood is small, as in Case 1 and Case 2 in the present series, the distinctive features are striking, so that Leary's explanation is unsatisfactory; furthermore it does not take into account the fact that after intracranial surgical operations, where there must be some subdural hæmorrhage at times, progressive false membranes do not form.

It would seem likely that in all instances where adhesions form between the dura mater and the brain, there has been a breakdown of the barrier between neural and somatic tissues, and that an essential underlying state for the production of so-called progressive subdural hæmorrhage is that the barrier between neural and somatic tissues should remain intact. In this regard Trotter's statement (1926), that the blood and blood-vessels belong to the somatic side of the frontier, should be noted.

Conclusions.

(1) The lining of the dura mater differs both in structure and in function from the lining of serous membranes.

(2) The lining of serous membranes is composed of a single layer of conspicuous mesothelial cells which, ordinarily at least, do not exercise phagocytic properties, and do not form fibrous tissue.

(3) The dura mater is lined by modified connective tissue cells, flatter and less clearly defined than the mesothelial cells lining serous membranes, and different from the ordinary connective tissue cells of the dura mater. The lining cells of the dura mater may exercise active phagocytic properties and ingest blood pigment in considerable amounts, or may develop through fibroblasts into fibrous tissue.

(4) Subdural hæmorrhagic false membranes are not due to inflammation, but to irritation of the cells which line the dura mater by extravasated blood. The extravasation of blood occurs first, and the blood stimulates the lining cells of the dura mater to form the false membrane.

(5) When blood is extravasated into the subdural space the reaction of the cells lining the dura mater is essentially the same whether the extravasation is small or large, and whether it is associated with trauma or disease of any kind.

(6) Delicate hæmorrhagic membranes, cysts, and relatively fibrous membranes are essentially of the same nature.

(7) The distinctive features of the reaction are: (*a*) it results in the formation of a false membrane loosely attached to the dura mater from which it is easily reflected leaving a relatively smooth surface; (*b*) the false membrane is quite free from the arachnoid mater which takes no part in its formation; (c) the condition, instead of leading to cicatrization and the formation of adhesions or a scar, tends to be progressive.

(8) It is suggested that the essential condition responsible for the distinctive features of subdural hæmorrhagic false membranes, as contrasted with subdural hæmorrhages followed by adhesions, may be related to the neuro-insulation theory of Trotter, and depend on a maintenance of the barrier between neural and non-neural tissues.

(9) It is further suggested that the formation of subdural hæmorrhagic false membranes, with their characteristic and distinctive features, may represent one application of a general law—namely that "The tissues of a part develop to meet its needs; and if the main needs of the part are highly specialized, some of the attributes necessary to meet its ordinary needs may be rendered inadequate."

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PLATE XV.

FIG. 1.—Normal parietal peritoneum with lining of mesothelium. × 200.

FIG. 2.—Normal parietal pericardium with lining of mesothelium. × 200.

FIG. 3.—Pericardium (visceral)—early pericarditis. Swollen mesothelial cells are to be seen near the mid-line. × 200.

FIG. 4.—Normal dura mater cut at right angles to the surface. The lining cells (to the right) are inconspicuous. × 200.

FIG. 5.—Normal dura mater cut slightly obliquely. The lining cells are to be seen on the right. × 200.

FIG. 6.—Normal dura mater cut obliquely. As in fig. 5 the lining cells (to the right) are seen to differ from the cells of the connective tissue proper.

FIGS. 1, 2, 4, 5 and 6 are all photomicrographs of tissues from the body of the one man (aged 25 years).

PLATE XVI.

FIG. 7 (*Case* 1).—A drawing which shows the delicate false membrane on the deep surface of the dura mater, from the upper part of which the membrane has been partly reflected.

FIG. 8 (*Case* 1).—A delicate membrane is to be seen on the right, attached to the under surface of the dura mater. × 200.

FIG. 9 (*Case* 1).—The delicate membrane on the right is at the earliest stage of its formation. The arrow points to a cell laden with hæmosiderin; unpigmented lining cells are to be seen above and below it. × 200.

FIG. 10 (*Case* 1).—The flat surface of a small reflected flake of membrane is to be seen. × 200.

PLATE XVII.

FIG. 11 (*Case* 2).—Part of the affected dura mater. In the upper part of the illustration portion of the false membrane is seen to have been reflected downwards.

FIG. 12 (*Case* 2).—The false membrane in its deeper part contains intact red blood cells, in its superficial part the cells that compose it form thin layers which tend to become separated from one another. × 280.

FIG. 13 (*Case* 2).—The false membrane is here more compact. × 290.

FIG. 14 (*Case* 2).—Portion of the false membrane which looked hæmorrhagic to the naked eye. × 220.

PLATE XVIII.

FIG. 15 (*Case* 3).—Scattered hæmorrhages are seen to be present on the deep surface of the dura mater. Where these are not present, the deep surface of the dura (except on the extreme right) has a somewhat dirty look, due to the presence of a delicate false membrane.

FIG. 16 (*Case* 3).—The portion of fig. 15 indicated by the arrow is here shown on a larger scale.

PLATE XIX.

FIG. 17 (*Case* 3).—Red blood cells and primitive leucocytes (nucleated) are present close to the dura mater, and connective tissue cells are conspicuous near the free surface of the false membrane. × 270.

FIG. 18 (*Case* 3).—A horizontal section through the false membrane near the free surface. × 255.

FIG. 19 (*Case* 3).—One of the areas which looked hæmorrhagic to the naked eye. × 165.

FIG. 20 (*Case* 3).—Portion of parietal pleura showing changes superficial to and deep to the connective tissue zone of the pleura. × 85.

PLATE XX.

FIG. 21 (*Case* 4).—The membrane is fairly firm and dense for the most part. Near the dura mater (above) it is looser in texture. × 65.

FIG. 22 (*Case* 5).—The membrane is composed for the most part of fibroblastic connective tissue. × 235.

FIG. 23 (*Case* 6).—The left side of the illustration represents the surface of the membrane which was loosely attached to the dura mater. The vascular channels are well formed. × 75.

FIG. 24 (*Case* 6).—In this part of the membrane the vascular channels have delicate walls, some of which have ruptured, thus leading to extravasation of blood. × 195.

PLATE XXI.

FIG. 25 (*Case* 7).—The extravasated blood lies between two layers of false membrane, both of them deep to the dura mater.

FIG. 26 (*Case* 7).—This shows the margin of the large flat space filled with blood clot. The junction of inner and outer layers of false membrane is evident. The dura mater is on the left. × 45.

PLATE XXII.

FIG. 27 (*Case* 8).—The empty cyst can be seen between the left cerebral hemisphere and the dura mater.

FIG. 28 (*Case* 8).—The outer wall of the cyst. The line of contact with the dura mater is shown at the upper limit of the illustration. The lumen of the cyst is below the cellular inflammatory zone. × 105.

FIG. 29 (*Case* 8).—The inner wall of the cyst. The lumen of the cyst is on the left, the surface of the wall which rested on the arachnoid is on the right. × 165.

PLATE XXIII.

FIG. 30 (*Case* 8).—Portion of the outer wall near its junction with the inner wall at the margin of the cyst. This portion if traced laterally links up with the portion to be seen in the upper half of fig. 28. × 100.

FIG. 31 (*Case* 8).—Portion of the outer wall near its junction with the inner wall at the margin of the cyst. Dilated vessels filled with blood dominate the picture. × 130.

FIG. 32 (*Case* 8).—Portion of the damaged cerebral tissue underlying the cyst.

FIG. 33 (*Case* 8).—Showing complete destruction of cerebral tissue underlying the cyst. × 150.

PLATE XXIV.

FIG. 34 (*Case* 9).—A drawing of the gross specimen showing the subdural fibrous false membrane.

FIG. 35 (*Case* 9).—The fibrous false membrane containing hæmosiderin is to be seen on the deep surface of the dura mater. × 55.

PLATE XV.

FIG. 1.

FIG. 2.

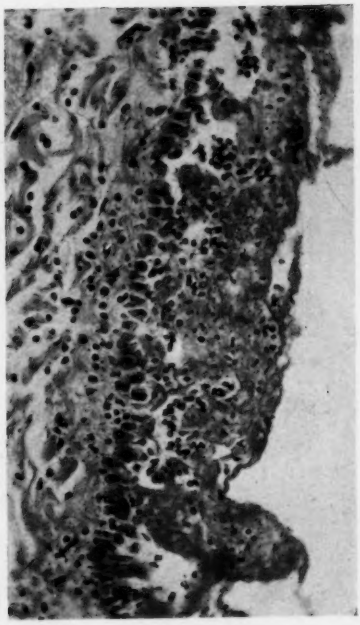

FIG. 3.

FIG. 4.

FIG. 5.

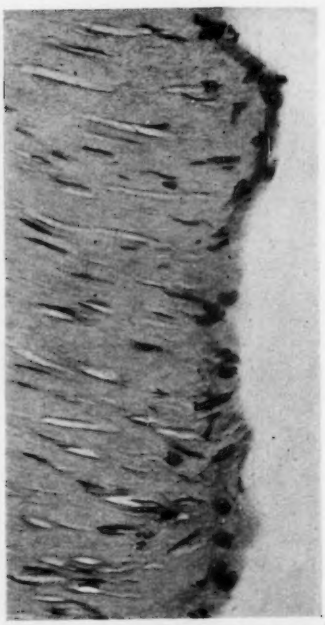

FIG. 6.

To illustrate article by Keith Inglis.

PLATE XVI.

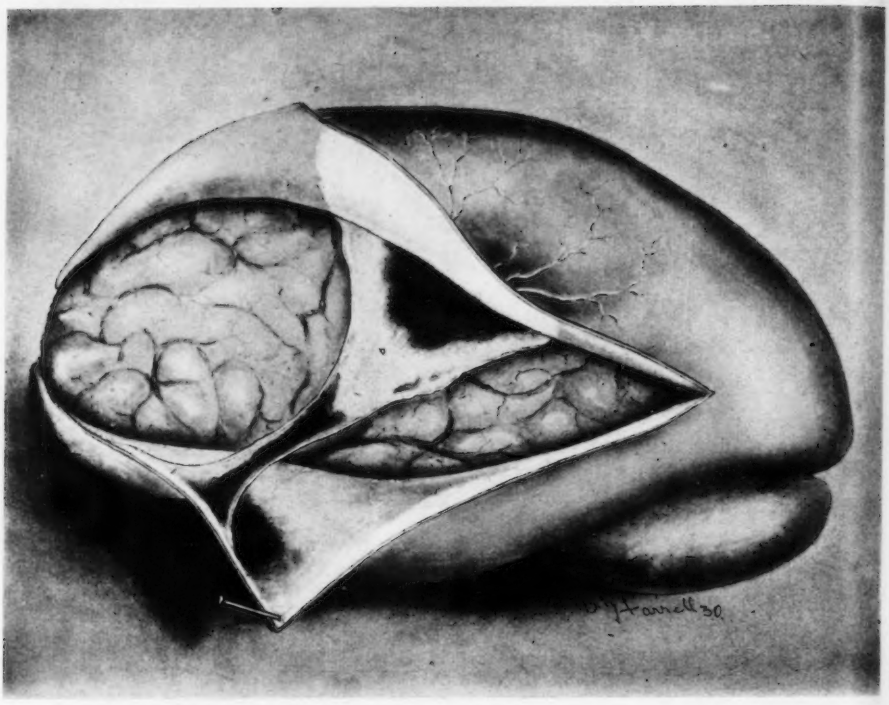

FIG. 7.

FIG. 8.

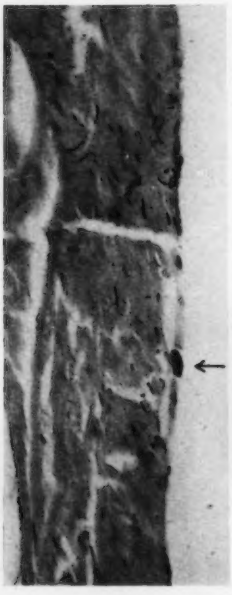

FIG. 9.

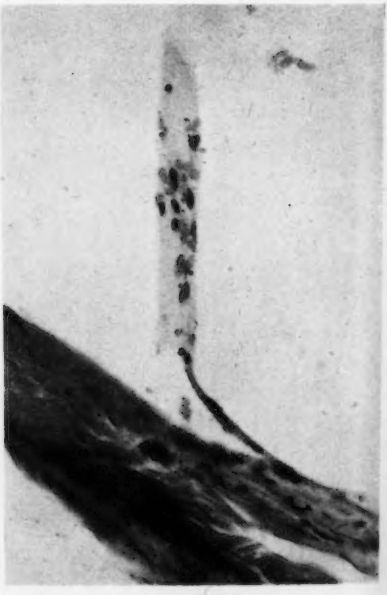

FIG. 10.

To illustrate article by Keith Inglis.

PLATE XVII.

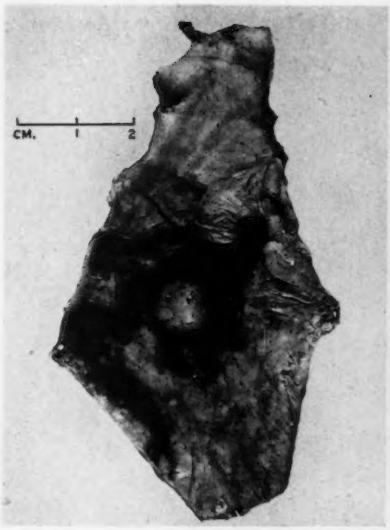

FIG. 11.

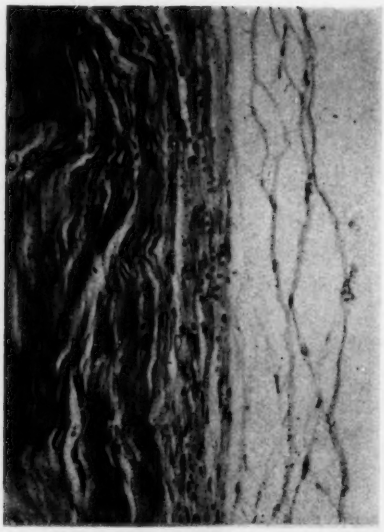

FIG. 12.

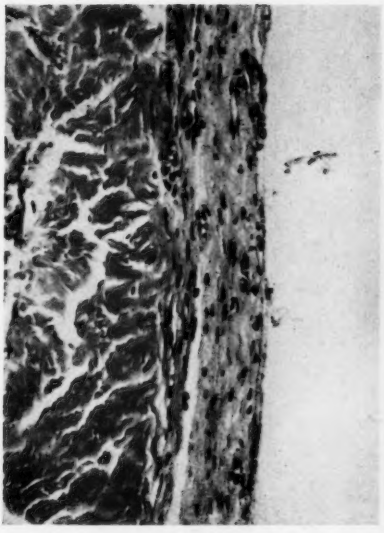

FIG. 13.

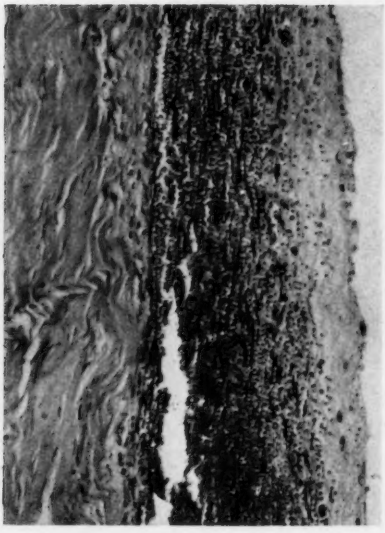

FIG. 14.

To illustrate article by Keith Inglis.

PLATE XVIII.

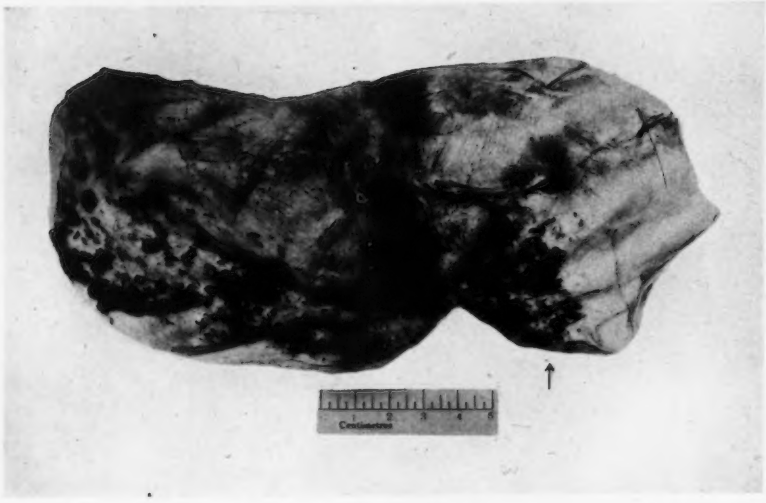

FIG. 15.

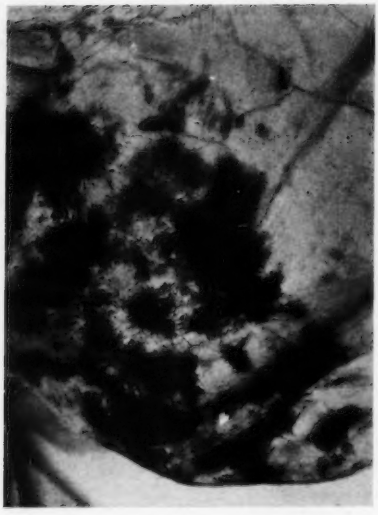

FIG. 16.

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PLATE XIX.

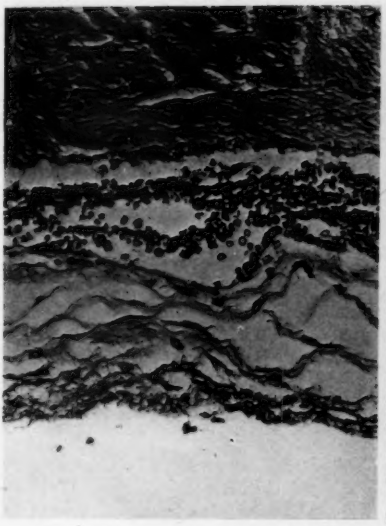

FIG. 17.

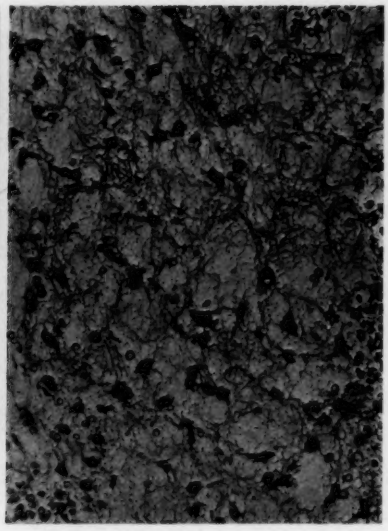

FIG. 18.

FIG. 19.

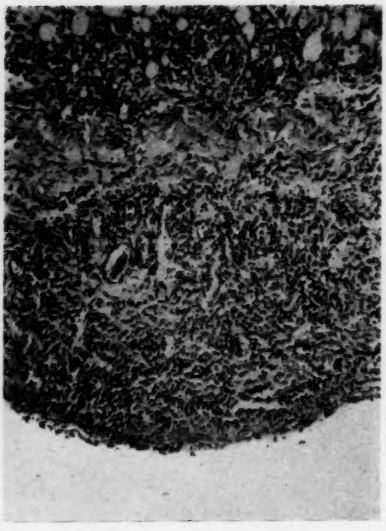

FIG. 20.

To illustrate article by Keith Inglis.

PLATE XX.

FIG. 21.

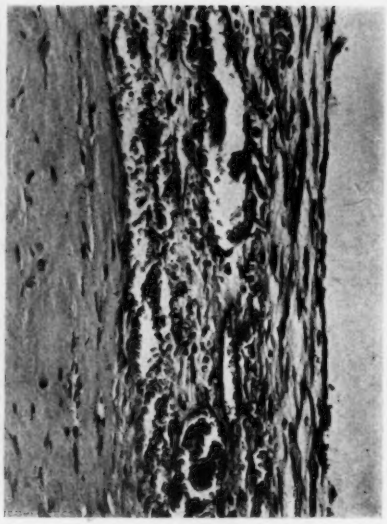

FIG. 22.

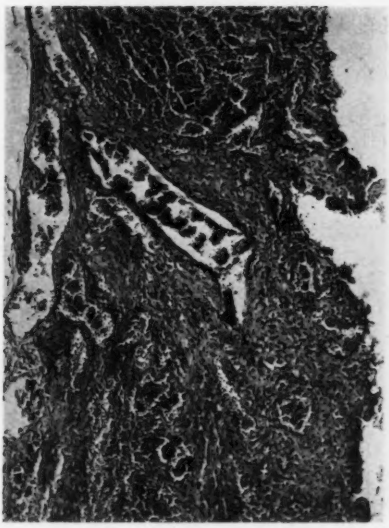

FIG. 23.

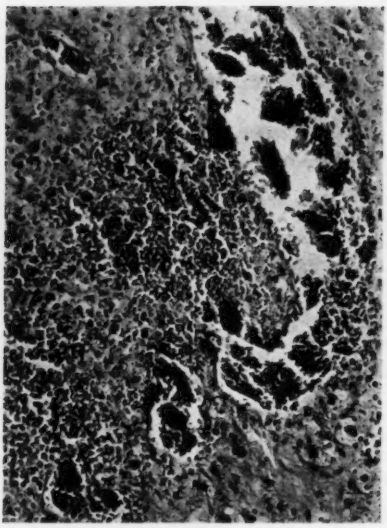

FIG. 24.

To illustrate article by Keith Inglis.

PLATE XXI.

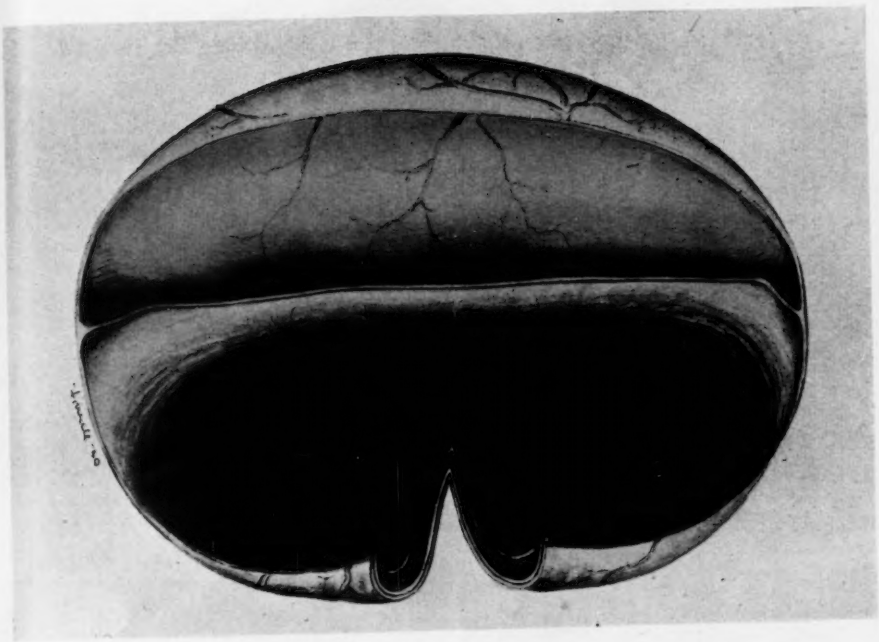

FIG. 25.

FIG. 26.

To illustrate article by Keith Inglis.

PLATE XXII.

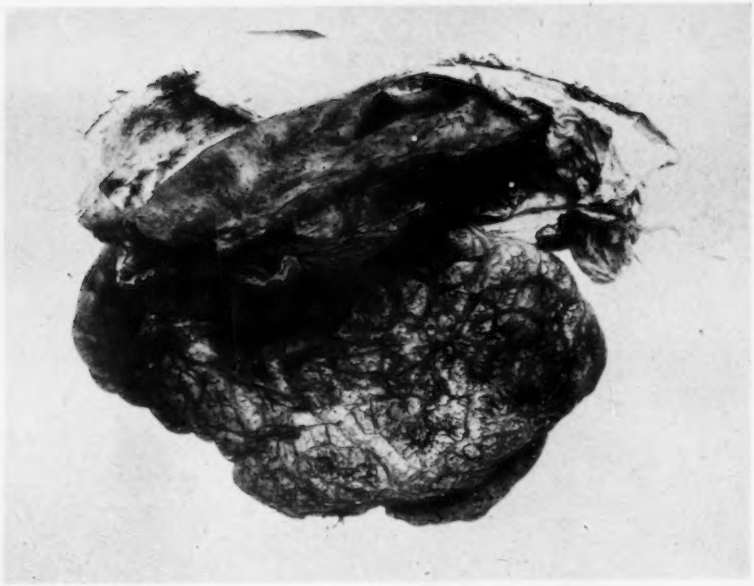

FIG. 27.

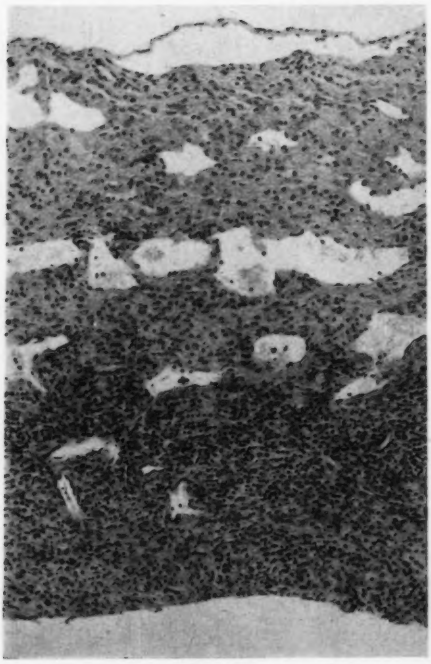

FIG. 28.

FIG. 29.

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PLATE XXIII.

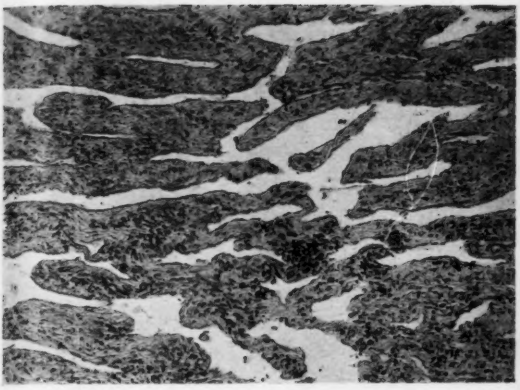

FIG. 30.

FIG. 32.

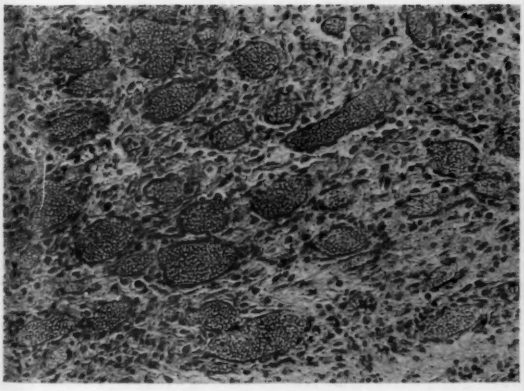

FIG. 31.

FIG. 33

To illustrate article by **Keith Inglis**.

PLATE XXIV.

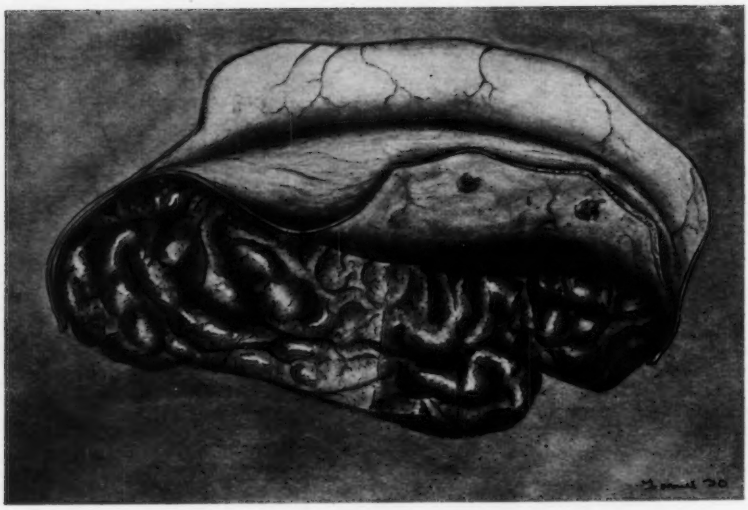

FIG. 34.

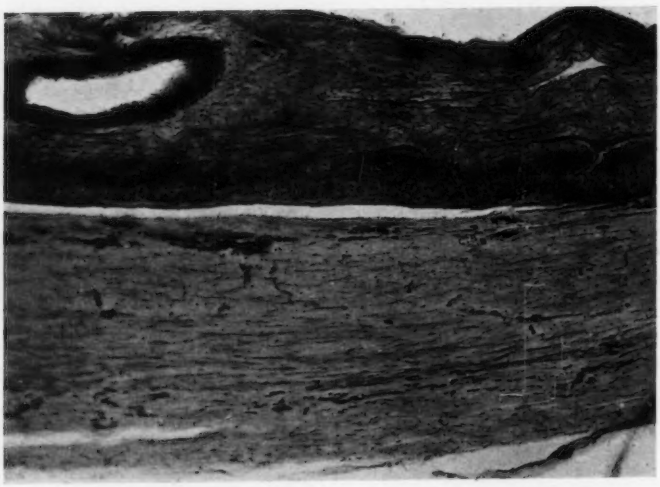

FIG. 35.

To illustrate article by Keith Inglis.

FIBRE CONNECTIONS OF THE SUBTHALAMIC REGION AND THE CENTRO-MEDIAN NUCLEUS OF THE THALAMUS.

BY P. GLEES AND P. D. WALL[1]

University Laboratory of Physiology, Oxford.

Introduction.

It has recently been shown that many of the connections of the basal ganglia run in the subthalamic region (Glees, 1945). Since this region contains several nuclei such as the subthalamic nucleus whose connections are incompletely known, we have carried out an experimental analysis of their afferent and efferent pathways. Our attention was also directed to the area by the growing amount of clinical and pathological evidence that hemichorea in man is associated with lesions of the subthalamic nucleus. In the course of our experiments observations on the fibre connections of the centro-median nucleus have been gathered which show an intimate relationship of this nucleus with the subthalamic region. These findings have therefore been included in this communication.

The subthalamic region contains the zona incerta and the fields of Forel, the nucleus subthalamicus or corpus Luysii, the nucleus ruber, substantia nigra and the entopeduncular nucleus. It is bounded ventrally by the hypothalamus, dorsally by the thalamus and laterally by the internal capsule.

Review of the Literature.

The earliest physiological work on the function of the subthalamic region by Karplus and Kreidl (1913) has been criticized by Ranson because the smooth muscle responses which were thought to be specific for the region are known to be a general response from a very large part of the brain. However, Hinsey, Ranson and McNattin (1930) found that if serial sections of the brain are made, the transition from the animal capable of walking to the decerebrate animal occurs when the subthalamic nucleus is cut off from the brain-stem. Morgan (1927) and Mella (1923) also confirm this finding.

[1] Scholar of Christ Church, Oxford.

Neuro-pathological observations indicate that the nucleus subthalamicus or corpus Luysii has an influence upon movement. In a great number of cases it has been found that a lesion of the nucleus is associated with violent hemichorea (Canfield and Putnam, 1884; Economo, 1910; Fischer, 1911; Campora, 1922; Pette, 1922; Jakob, 1923; Spatz, 1927; Schaffer, 1928; Jakob, 1928; v. Santha, 1928 and 1932; Pelnar and Sikl, 1928; Uiberall and Sanet-Ambrus, 1931; and Martin and Alcock, 1934). In most of these cases destruction was extensive but in one (Matzdorff, 1927) it was restricted to the subthalamic nucleus and in only one case of hemichorea of acute onset was the condition not associated with damage to the nucleus (Wilson, 1914), and this was an atypical case. Stimulation of the region produces running movements in the cat (Waller, 1940) thus confirming the less detailed work of Ectors, Brookens and Gerard (1938), and Masserman (1938).

We may therefore conclude that the region contains important pathways concerned in the mediation of movement, and it is possible that the cortical suppressor system which is known to control also the spinal motor neurones sends fibres through the area.

Anatomy.

The biconvex lens-shaped nucleus is a unitary cell mass according to Papez (1942) and Rioch (1929), but Kodoma, quoted by Roussy and Mosinger (1935), stated that it has two parts, a large-celled lateral part and a small-celled medial part. There is some pathological evidence in favour of a somatotopic differentiation (Martin and Alcock, 1934), which suggests that the antero-lateral part of the nucleus is concerned with movement of the face, but histological differentiation of such an area does not seem possible. The main afferent supply to the subthalamic nucleus has been shown by many to run from the striatum via the fasciculus subthalamicus (Mahaim, 1893; von Monakow, 1895, 1905, 1909, 1926; Probst, 1903; Grünstein, 1911; C. and O. Vogt, 1920; Jakob, 1925; Reise, 1924; Foix and Nicolesco, 1925; Rioch, 1929; and Papez, 1938). There is evidence that these fibres are of globus pallidus origin only (Wilson, 1914; Ranson, 1939; Probst, 1903; and Edinger and Fischer, 1913).

Fibres from the substantia nigra to the subthalamic nucleus have been described by Mirto, 1896; Bauer, 1909; Sano, 1910; Kodama, 1929; and Rioch, 1929. Kappers states that there are fibres running from nucleus ruber to the subthalamic nucleus. In lower mammals a very definite tract, the tractus opticus accessorius, has been shown (Kölliker, 1896; Loepp, 1912; and Tsai, 1925), but there is no sign of this in the higher mammals.

There has been considerable controversy as to whether the cortex sends efferent fibres to the subthalamic region: their presence is claimed by Dejerine (1901), Foix and Nicolesco (1925), and Mettler (1945), but others have been unable to demonstrate these fibres (Monakow, 1909, 1910; Minkowski, 1923; Rioch, 1929 and Papez, 1942). However, it has been pointed out by Levin (1944) that the cortico-rubral fibres described by many observers pass through the subthalamic nucleus, and these may be the fibres which some neurologists have thought to end in the subthalamic nucleus.

Other afferents reported are those from the lateral nucleus of the hypothalamus (Roussy and Mosinger, 1935), the opposite subthalamic nucleus (Tsai, 1925; Gurdjian, 1927; Rioch, 1929) and the opposite lenticular nucleus (O. Vogt, 1904; Marburg, 1910; Flechsig, 1921; Pollak, 1922; and Darkschewitsch and Pribytkow, 1891).

The efferent connections have been shown to run mainly into the lenticular fasciculus of Forel (Greving, 1923; Rioch, 1929; and Morgan, 1927), and into the substantia nigra or more especially into a medial group of cells [n. pigmentosus subthalamo-peduncularis or Jacobsohn's group].

It has also been stated by Papez (1938) that efferents pass to the tegmentum, and, in some earlier work, that there were projections on to the pons and cerebellum (Papez, 1929), but in his later work Papez has not maintained this view, while Rioch (1929) failed to find any of these fibre tracts. Efferents pass to the red nucleus (Rioch, 1929; Kölliker, 1896). Thus it may be concluded that there was very little information in the literature to indicate that the subthalamic nucleus is anything but a relay station for descending fibres.

Experimental Method and Histological Technique.

Five young macaque monkeys (*Macaca mulatta*) were used in these experimental studies. Anæsthesia was induced by intraperitoneal nembutal in a dose of 35 mg./kilo. The head was completely shaved and a broad copper electrode was fixed to the lumbar dorsal region by a bandage. The head was firmly clamped in a Souttar-Beattie apparatus with the skull fixed at the posterior end of each zygomatic arch and by a clamp on the nose and upper teeth. Care was taken to ensure that the line joining the external auditory meati and the line joining the occipital protuberance with the orbital margin of the frontal bone were horizontal. The scalp was reflected by a right median sagittal incision and the bone exposed. A window was cut in the bone by a dental drill and the dura was opened and reflected. Bleeding was controlled by bone wax, macerated muscle and fibrin foam but the use of the dental drill ensured very little bleeding

Area 4 was identified by low voltage stimulation of the cortex and the observation of hand, arm and leg movement. A thin insulated needle held in an adjustable rack and pinion clamp on the Souttar-Beattie apparatus was then inserted vertically through a point 4 mm. anterior to the central fissure and 6 mm. from the mid-line

and lowered until the non-insulated tip of the needle was 29 mm. below the surface. A high frequency, high voltage current was then passed for ten to twenty seconds and the needle was withdrawn. The dura was closed and the scalp sutured by a multiple discontinuous linen suture. It was found unnecessary to replace the removed bone.

After twenty-one to thirty days the animals were killed and the brains removed and stained by the Swank-Davenport method (Glees, 1943), and examined after serial sectioning and embedding in celloidin.

The following are the abbreviations used in the diagrams and figures:—

c.g.	central grey.	o.tr.	optic tract.
c.m.	centro-median nucleus.	pall.	globus pallidus.
c.i.	capsula interna.	put.	putamen.
c.p.	cerebral peduncle.	r.n.	red nucleus.
d.m.	dorso-medial.	s.	subthalamic nucleus.
l.g.b.	lateral geniculate body.	s.nig.	substantia nigra.
m.b.	mammillary body.	th.	thalamus.
m-th.t.	mammillo-thalamic tract.	z.i.	zona incerta.

Case Records.

*M.S.L.*2. Op. 30.8.45. Killed 24.9.45.

Localization of lesion.—The lesion involves the medial part of the lateral thalamic nucleus and the inner third of the subthalamic nucleus. The tip of the lesion reaches the junction of subthalamic nucleus and substantia nigra.

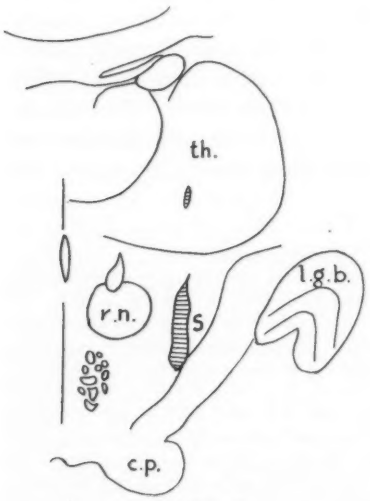

Fig. 6

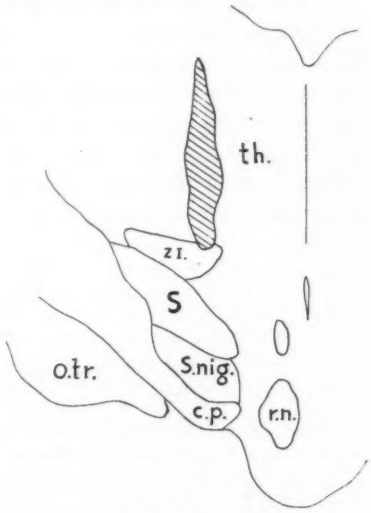

Fig. 7

Course of the degenerated fibres.—Numerous degenerated fibres from the lateral thalamic nucleus ascend to the cortex via internal capsule. Degenerated fibres enter Forel's field and scatter within the red nucleus between it and the substantia nigra and as far medial as the interpeduncular nucleus.

Fine degenerated fibres cross the mid-line within the interthalamic commissure to enter the opposite lateral thalamic nucleus. Further commissural fibres can be found degenerating within the supra-mammillary commissure to the opposite subthalamic nucleus and in the ventral tegmental decussation to the opposite red nucleus. Numerous degenerating fibres from the lateral thalamic nucleus cross the internal capsule and enter internal and external division of the pallidum. Very fine degenerating fibres from the subthalamic nucleus pierce the internal capsule and terminate within the internal division of the pallidum. A distinctly staining bundle of degenerating fibres enters the globus pallidus originating from the zone of injury between the subthalamic nucleus and the substantia nigra. Fibres can be traced into the centro-median nucleus and as far caudally as the mid-brain where the superior colliculus receives some degenerated fibres (*see* Plate XXV, Figs. 1, 2, 3).

*M.S.L.*3. Op. 31.8.45. Killed 5.10.45.

Localization of lesion.—The needle having passed through the precentral gyrus entered the lateral thalamic nucleus and caused a lesion of the tip of the internal pallidal division and the neighbouring optic tract. The lesion extends further caudally and injures the lateral border of the subthalamic nucleus and the internal capsule.

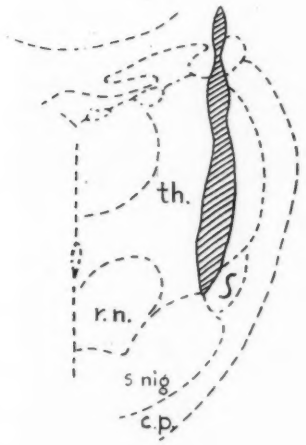

FIG. 8

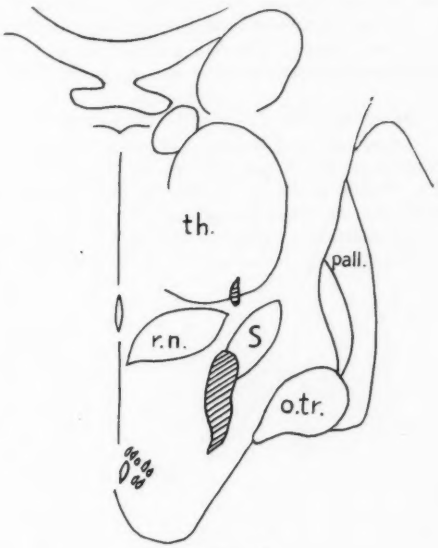

FIG. 9

Course of degenerated fibres.—Fibres from the internal pallidal division form the ansa and fasciculus lenticularis and project upon the lateral thalamus and hypothalamus as described previously (Glees, 1945). At the level of the subthalamic lesion numerous fibres emerge from the lateral aspect of the subthalamic nucleus and enter the pallidum. Medially from the subthalamic nucleus distinct degeneration can be traced into the nuclear group dorsal to the medial portion of the

substantia nigra. Some fibres enter the red nucleus and others cross the mid-line in the ventral tegmental decussation. Degenerated fibres can be followed into the centro-median nucleus and into the substantia nigra. Both oculomotor nuclei contain fine Marchi's granules.

M.S.L.5. Op. 3.10.45. Killed 8.11.45.

Localization of lesion.—The needle passed through the motor cortex and lateral nucleus of the thalamus and caused a lesion of the medial border of the subthalamic nucleus and the lateral portion of the substantia nigra.

Course of degenerated fibres.—Fibres ran from the injured part of the subthalamic nucleus into the pallidum. Some degenerated fibres from Forel's field reach the red nucleus and cross within the tegmental decussation to the opposite red nucleus. From the injured substantia nigra numerous fibres ascend to enter the superior colliculus of the same and opposite side and enter the centro-median nucleus of the same side.

M.S.L.6. Op. 5.10.45. Killed 16.11.45.

Localization of lesion.—The needle passed through the motor cortex, and lateral nucleus of the thalamus and caused a lesion of Forel's field H.1, the subthalamic nucleus and the lateral nucleus of the substantia nigra.

Course of degenerated fibres.—The main fibre connexions are identical to those described above. The fibres from the substantia nigra to the superior colliculus and centro-median nucleus are, however, particularly well outlined.

M.S.L.10. Op. 24.2.46. Killed 12.3.46.

Localization of lesion.—Following a small subdural hæmatoma there was cortical damage of area 4, possibly area 6, around the entry point of the penetrating needle. The needle track, by following the internal medullary lamina of the thalamus damaged the outer margin of the medial nucleus and the anterior portion of the centro-median nucleus. Field H.1 of Forel is damaged but the lesion does not extend into the zona incerta, or the field H.2 of Forel or the subthalamic nucleus.

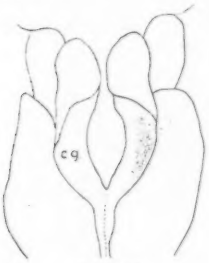

FIG. 10

FIG. 11

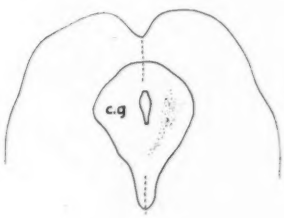

FIG. 12

FIG. 10.—M.S.L.10 shows the extension of the tract to the central grey at the level of the posterior thalamus. The whole of the right side of the central grey is filled with degenerating fibres at this level.

FIG. 11.—M.S.L.10: Tract to the central grey at the level of the posterior commissure.

FIG. 12.—M.S.L.10 shows the tract in the central grey at the level of the posterior colliculus.

Course of degenerated fibres.—Fibres run from the region of incidental cortical damage to the internal capsule and can be followed to the spinal cord. The red nucleus is supplied by fibres from Forel's field. At the level of intended injury distinctly grouped fine fibres run into the central grey. The dorsal quarter of the subthalamic nucleus is traversed by fine fibres running between the internal capsule

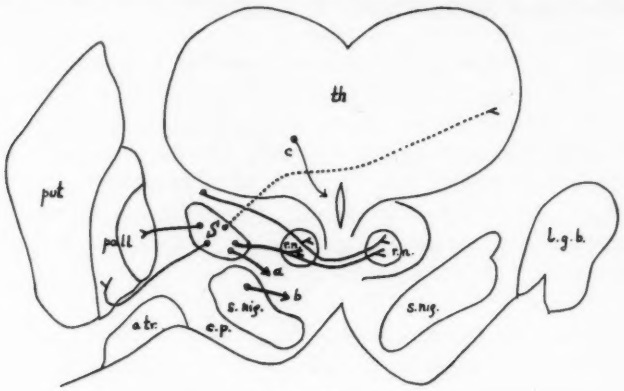

FIG. 13

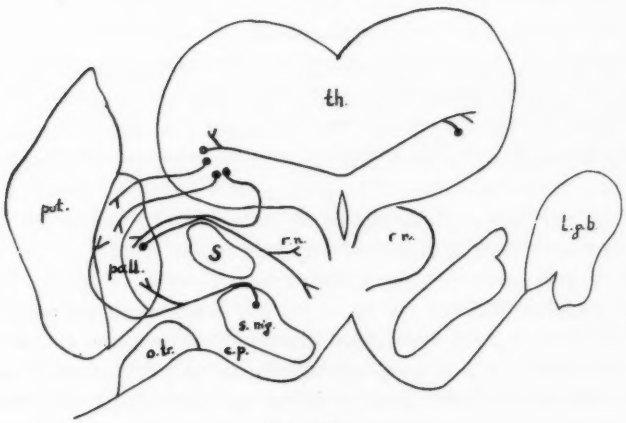

FIG. 14

FIG. 13.—Diagram of the fibre connections of the subthalamic region: (*a*) Indicates the fibres to a cell group dorso-medial to substantia nigra and the interpeduncular nucleus. (*b*) Indicates the fibres to the anterior colliculus and the centro-median nucleus of the thalamus. (*c*) Indicates the fibres to the central grey.

FIG. 14.—Diagram of fibre tracts which pass through the subthalamic region without originating from the region. The fibres running across the mid-line originate in the lateral nucleus of the thalamus and cross in the interthalamic commissure to the opposite side.

and the red nucleus. A small number of thick fibres runs through more ventral parts of the nucleus and may be aberrant capsular fibres. Capsular fibres *en passage* pass through the dorso-lateral portion of the substantia nigra. A few fine fibres end in the superior colliculus. Fibres of fine calibre enter from the injured thalamus into Forel's field H.1 and run through field H.2 into the globus pallidus by piercing the internal capsule (*see* Plate XXVI, figs. 4 and 5).

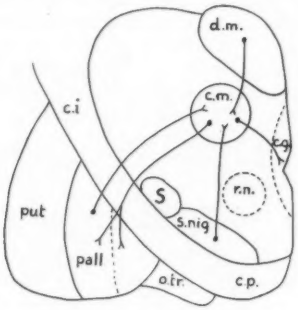

FIG. 15

FIG. 15.—The diagram shows the suggested connections of the centro-median nucleus with other structures.

DISCUSSION.

When surveying the data relevant to the connections of the subthalamic area it proves difficult to assess the true value of the results as described in the review of the literature. This difficulty increases when one realizes that the subthalamic area is also an important region for the passage of fibre tracts to the thalamus. The great wealth of fibres streaming through the region partially explains the many contradictory statements about the actual connections within the subthalamic region itself.

The examination of our experimental material is greatly facilitated by the previous study of the basal ganglia connections (Glees, 1945). In this investigation some knowledge was obtained as to the extent to which the subthalamic area is supplied or crossed by pallidal efferents. Some of these pallidal efferents actually pierce the subthalamic nucleus in their course to the tegmental field of Forel and are cut in a subthalamic lesion.

Afferents to the subthalamic nucleus.—Recent work by Ranson and Ranson (1942), Mettler (1945) and Glees (1945) establishes that the pallidum projects upon the subthalamic nucleus. Ranson and Ranson (1942) favour the view that the external division of the pallidum is the main source of these fibres. However, Mettler (1945) and Glees (1945) demonstrated that both external and internal pallidal divisions contribute to this connection.

Fibres from the substantia nigra converge at the ventral surface of the subthalamic nucleus, and some fibres terminate in the nucleus thus confirming the observations reported in the literature. The further course of these fibres will be discussed later. The statement in the literature that fibres from the cortex and fibres from the nucleus ruber reach the subthalamic nucleus cannot be checked for the simple reason that in our material cortical injury was always combined with injury to efferents from the pallidum (with the exception of M.S.L.10) and no lesion within the red nucleus was attempted. However, Sachs (1909) in his careful study reports that no fibres from the red nucleus enter the subthalamic nucleus (Case Rh.211). Mettler (1945) favours the view that the cortical efferents reach the subthalamic nucleus via the fasciculus thalamicus. In M.S.L.10 considerable degeneration from area 4 can be observed but no conspicuous Marchi granules are located apart from fibres which pass through the nucleus.

Efferent connections of the subthalamic nucleus.—It is surprising to find that no long projection system arises from the nucleus. Considering the large size of the nerve cells within the greater part of the nucleus one would expect a long-distance connection. However, the only clearly demonstrable pathway of any length from the subthalamic nucleus terminates within the globus pallidus by crossing the internal capsule. We may recall here the following statement of Dejerine (1901), "En résumé, le corps du Luys (subthalamic nucleus) dépend essentiellement du corps strié; il dégénère chaque fois que le globus pallidus, le putamen et le noyau caudé sont détruits."

There are indications that the Marchi granules within the red nucleus, its surrounding fibres and the ventral tegmental decussation are increased when pallidal and subthalamical lesions are combined. The impression is also gained that the medial portion of the substantia nigra contains more products of degenerating myelin than in a pure pallidal injury. However, the same pathways (to substantia nigra and nucleus ruber) can be demonstrated after pallidal lesion but the present study favours the view that these pallidal pathways are reinforced by subthalamic contributions.

This conclusion is confirmed by Mettler (1945). He observes that the subthalamic nucleus gives rise to a group of fibres, the subthalamic-pre-rubral fibres. These fibres pass further caudally towards the interpeduncular nucleus. The subthalamic nucleus gives off some fibres which ascend into the ventral nucleus of the thalamus and the centro-median

nucleus of the same side. Some fibres decussate in the interthalamic commissure and pass to the opposite thalamus.

Commissural fibres of the subthalamic nucleus.—The subthalamic nucleus contributes to the supra-mammillary commissure and its caudal extension, the ventral tegmental decussation. These crossing fibres reach the red nucleus and the subthalamic nucleus of the opposite side.

Afferent connections of the substantia nigra.—According to Mettler (1945), cortico-nigral fibres originate in area 6 and end in the pars diffusa of substantia nigra. In one of our monkeys, M.S.L.10, there was some injury to area 6 of the cortex without damage to the subthalamic structures except the field H.1 of Forel. In this case fibres which originate in the internal capsule sweep through the dorso-lateral part of the substantia nigra but do not appear to terminate there.

Efferent connections of the substantia nigra.—Injury to the substantia nigra causes degeneration of a distinctly staining fibre bundle which passes ventrally to the subthalamic nucleus and enters the ventro-medial part of the pallidum. Some efferents from the subthalamic nucleus join these nigral fibres and also terminate in the pallidum. Most noteworthy, however, is the existence of a nigral projection upon the centro-median nucleus. This connection has not been demonstrated hitherto and deserves all the more attention because it throws some light on the function of this nucleus. The connections of the centro-median nucleus are hardly known. Walker (1938) states that this nucleus has no cortical connection and Mettler (1945) believes that the nucleus is intimately related to the basal ganglia. Our material with injury to pallidal efferents shows degenerated fibres entering the centro-median nucleus; furthermore Mettler (1945) observed fibres from the centro-median to the pallidum. It seems most likely, therefore, that the centro-median nucleus is essentially not a typical thalamic component in the sense that the nucleus receives no important proprioceptive or exteroceptive afferents and does not project upon the cortex. The function of the centro-median nucleus, according to our observations, is mainly a relay station for mid-brain impulses to the pallidum. It has to be seen how far this assumption, based upon the observation of the nigro-centro-median fibres and Mettler's demonstration of centro-median-pallidal fibres will find further confirmation. Furthermore, a connection of the nigra with the anterior colliculus of the same and opposite sides has been demonstrated. These fibres cross the medial fillet and ascend to the anterior colliculus. A similar observation has been made by Dejerine (1901) in his case "Richard."

It is difficult to say how many of these ascending nigral fibres originate

from the cortex as well; Sachs (1909) concludes from his experiments in the cat that cortico-tectal fibres exist. However, in the case of Dejerine's "Richard" the pyramidal system was completely absent and yet there were nigro-tectal fibres. In our case M.S.L.10 there were a few very fine fibres ending in the anterior colliculus and yet there were no changes in the substantia nigra or in the globus pallidus. We may therefore conclude that the subthalamic region supplies the majority of the fibres to the superior colliculus while the cortex supplies a small component only.

Afferent fibres to the central grey and the tegmental nuclei.—A striking observation in M.S.L.10 is the demonstration of a well-marked bundle of fine fibres running from the region where Forel's field H.1 fuses with field H.2. It runs medially and posteriorly through the subthalamic region to enter the central grey at the anterior level of the oculomotor nuclei. The fibres can be traced down to the mid-brain, pons and upper part of the medulla. They gradually diminish in number by terminating in their descent. Without any doubt the fibres belong to the fasciculus longitudinalis of Schütz recently discussed by Ingram (1940) and Le Gros Clark (1938). The general opinion seems to be that this bundle connects the hypothalamic centres, in particular the posterior hypothalamic region, with the tegmental nuclei and cranial nerve nuclei. Our case M.S.L.10 suggests that the dorso-medial nucleus and centro-median nucleus of the thalamus contribute to the bundle of Schütz. This thalamic source had been suggested by Schütz (1891) who claimed that the dorsal nuclei of the thalamus contributes to the bundle. Recent investigations (Meyer and Beck, 1945) not only show the connection of the dorso-medial nucleus of the thalamus with the frontal lobe, but suggest also the projection of the frontal lobe on to the dorso-medial nucleus. The importance of the dorso-medial nucleus by contributing directly or indirectly via the centro-median nucleus to the fasciculus longitudinalis dorsalis is considerable in view of its connections with the frontal lobe.

It seems likely that the subthalamic nucleus is part of the substantia nigra group of cells which has split off and has become closely associated with the globus pallidus. No long pathways ending in it have been shown as yet and it is probable that fine fibres run to it from the mid-brain. The suppressor system of the cortex has been shown to project on to the caudate nucleus and the globus pallidus (Glees, 1943, 1945), and it might be that the subthalamic nucleus reinforces this pathway since its main projection is on to the globus pallidus. The work of McCulloch, Graf and Magoun (1946) suggests that the spinal projection pathway of the suppressor system relays in the reticular substance of the medulla but there is as yet no histological confirmation of their physiological evidence.

SUMMARY.

Lesions have been made in the subthalamic region of the brain in five Macaque monkeys. The subthalamic nucleus is shown to project:—

(1) On to the external and internal division of globus pallidus.

(2) On to ipsilateral and contralateral red nucleus.

(3) On to ipsilateral and contralateral thalamus.

(4) On to a nucleus dorso-medial to substantia nigra.

The substantia nigra projects:—

(1) On to the globus pallidus.

(2) On to the centro-median nucleus.

(3) On to the anterior colliculus.

A pathway from the centro-median nucleus and the dorso-medial nucleus of the thalamus to the central grey passing through the subthalamic region has been demonstrated.

The authors wish to express their thanks to Mr. Marsland for taking the photomicrographs, to Miss Simms and Mr. Marsland for the preparation of the sections and to Dr. E. Glees for help in preparing the manuscript. We are very grateful to the Medical Research Council for the supply of monkeys.

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PLATE XXV.

FIG. 1.—M.S.L.2 shows the lesion extending to the medial border of the subthalamic nucleus. Fibres can be seen running medially to the red nucleus and to Jacobsohn's group ventral to the red nucleus and dorso-medial to the substantia nigra. The arrow indicates the fibres running in a compact bundle from the substantia nigra and the subthalamic nucleus to the globus pallidus.

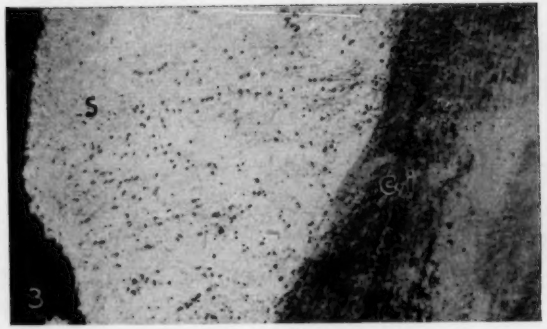
FIG. 2.—Shows the ending of fibres from the subthalamic nucleus in the red nucleus and ventral to this area in Jacobsohn's group. Fibres can be seen streaming across the mid-line in the interthalamic commissure.

FIG. 3.—Shows the fibres originating in the subthalamic nucleus running laterally to cross the internal capsule and end in the globus pallidus.

PLATE XXVI.

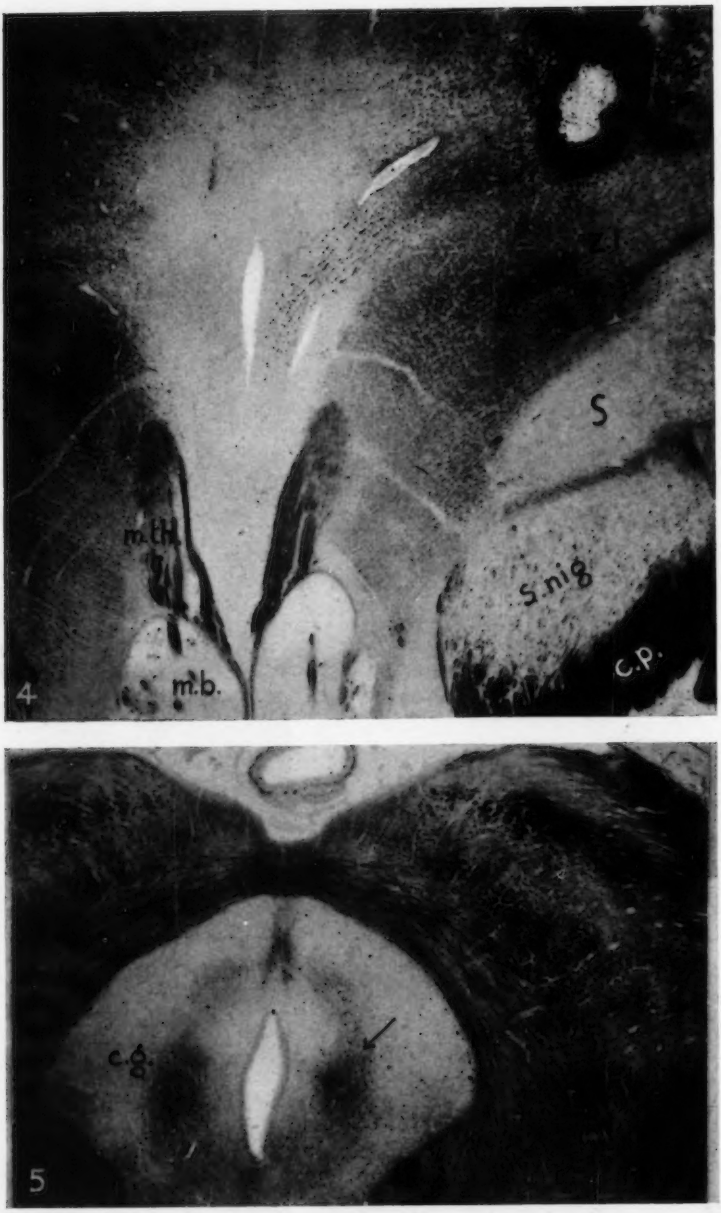
FIG. 4.—M.S.L.10: The origin of the fibre tract from the centro-median nucleus is shown to run from the nucleus destroyed by the lesion ventrally and medially to the periventricular region.

FIG. 5.—M.S.L.10 shows the tract whose origin is to be seen in fig. 4 running in the central grey at the level of the superior colliculi.



To illustrate article by P. Glees and P. D. Wall.

PLATE XXVI.



To illustrate article by P. Glees and P. D. Wall.

NUTRITIONAL NEUROPATHIES IN THE CIVILIAN INTERNMENT CAMP, HONG KONG, JANUARY, 1942—AUGUST, 1945.

BY DEAN A. SMITH.

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SEVEN syndromes loosely grouped together under the general title of "Nutritional Neuropathies" have so far been described as occurring in prisoners of war and internees in Japanese Camps in the Far East. Of these, three, namely spastic paraplegia (Kemball Price, 1946; Astley Clarke and Sneddon, 1946; Cruikshank, 1946), nerve deafness (Kemball Price, 1946; Astley Clarke and Sneddon, 1946) and Wernicke's encephalopathy (Cruikshank, 1946; Musselman, 1946) were not seen in the civilian camp in Hong Kong. Typical chronic dry beriberi occurred in only a few cases but there were many hundred cases each of subacute wet beriberi, sensory neuropathy or "burning feet" and amblyopia. It is possible that a description of these conditions, in particular in relation to each other, to dietary intake and to the incidence of other nutritional diseases, may be of some value as a contribution to the increasing volume of information on the basis of which the ætiology and inter-relationship of the diseases must be worked out.

Unlike all P.o.W. and many civilian camps, the civilian camp in Hong Kong had a population which was mixed both as regards sex and age. The total never varied widely from 2,500, of whom 1,300 were men, 900 women and 300 children under 16 years of age. All ages from birth to the eighties were represented. Overcrowding was extreme and sanitation poor. Facilities for laboratory investigation were absent and, owing to extreme shortage of supplies, treatment of all cases was difficult and of some impossible.

The dietary pattern in Japanese camps is now well known (Gupta, 1946; Astley Clarke and Sneddon, 1946; and others) and need not be described in detail. Overmilled, weevil-infested white rice was the staple; peanut oil, salt and sugar were small but fairly constant rations, buffalo beef in 1942 was replaced in 1943 by salt dried fish but the supply of animal food ceased altogether in 1944. The remainder of the rations were made up of vegetables, coarse greens, gourds and a few roots in season. Red Cross parcels were received on three occasions and during

the latter two years small but fairly regular supplies of soya beans, bran and rice polishings were received, provided by the local Red Cross organization.

The calculated value of the rations (based on the food tables of Platt, 1945; Read, Lee and Ch'eng, 1937; and Fixsen and Roscoe, 1940) are shown in Table I. It will be seen that by usually accepted standards (e.g. those of the National Research Council, 1943) they are deficient in all factors except vitamin C, carotenes and iron. In particular B complex vitamins are very low for such a high carbohydrate diet.

TABLE I.—AVERAGE NUTRITIONAL VALUE OF THE RATIONS PER PERSON PER DAY. AVERAGED BY YEARS.

		1942	1943	1944	1945
Protein ..	grm.	50·4	45·1	37·5	37·1
Fat	grm.	30·5	20·2	22·7	21·7
Carbohydrate	grm.	304·5	298·4	300·6	333·2
pro-Vitamin A	International units	10,307	10,347	6,910	5,998
Vitamin B_1 ..	mg.	0·48	0·40	0·30	0·33
Riboflavine ..	mg.	0·71	0·78	0·68	0·61
Nicotinic acid	mg.	9·0	8·9	8·0	6·9
Vitamin C ..	mg.	55·5	73·0	64·0	63·0
Calcium ..	grm.	0·237	0·257	0·317	0·335
Phosphorus ..	grm.	0·527	0·512	0·576	0·577
Iron	grm.	0·0118	0·0122	0·0115	0·0108
	Calories	1,689	1,552	1,566	1,679

Range : Calories per person per day—Low, 1,180, January, 1942.
Average for month—High, 1,986, July, 1942.

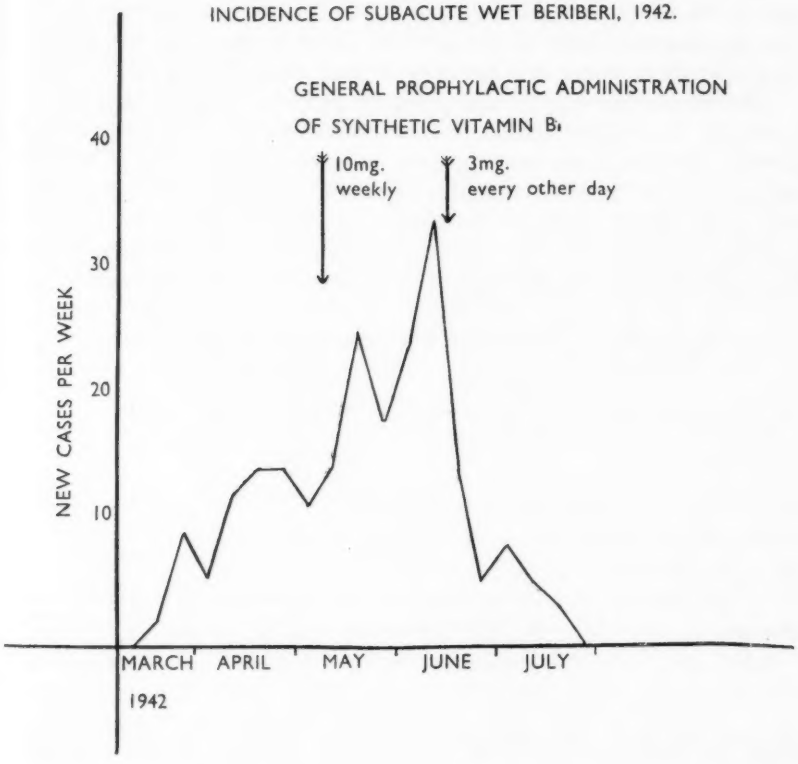
SUBACUTE WET BERIBERI.

The first nutritional disease to appear was subacute wet beriberi of which the first case was seen eighty-seven days after the Japanese occupation (cf. Fraser and Stanton, 1909, who suggested eighty to one hundred days for development of beriberi). A sharp epidemic (219 cases) followed and was terminated by the prophylactic administration of synthetic vitamin B_1 to the whole population—Graph 1.

It was only when supplies of B_1 for the general administration were exhausted that new cases reappeared and thereafter incidence remained high throughout the internment except for two short subsequent periods, October to December, 1944 and April to May, 1945, when further supplies enabled us to raise the vitamin B_1—carbohydrate ratio above the critical value for the development of symptoms, when, on each occasion, there was a satisfactory decline in incidence. The critical value for the B_1—carbohydrate ratio appears, from consideration of Graph 2, for this popu-

GRAPH I. CIVILIAN INTERNMENT CAMP, HONG KONG.

INCIDENCE OF SUBACUTE WET BERIBERI, 1942.



lation, diet pattern and environment to be in the region of 0·4 mg. per 1,000 carbohydrate calories. This value is higher than that arrived at by most recent workers, Keys, Henschel, Mickelsen and Brozek (1943), for instance, finding no clinical evidence of vitamin B_1 deficiency on an intake as low as 0·23 mg. per 1,000 total calories. On the other hand the value has been placed as high as 0·6 mg. per 1,000 calories by Williams, Mason and Wilder (1943).

In the absence of quantitative data concerning biosynthesis by intestinal bacteria, interpretation of dietary vitamin requirements is almost impossible. In the camp it is probable that several circumstances combined to reduce bacterial synthesis to a minimum, particularly the sudden

change from a European to a poor Asiatic type of diet, the prevalence of many types of diarrhœa and dysentery, and the dietary poverty in protein for the nutrition of the intestinal flora. For this reason it is probable that the dietary vitamin B_1 requirement found in the camp was higher than it would be under circumstances of more normal intestinal function.

The symptomatology of this group of patients, of whom there were in all 844, was entirely similar to that commonly seen among rice-eating peoples. In view of the contemporary presence of many cases of famine œdema and of "neuritic" manifestations the diagnosis of beriberi was only made in the presence of œdema, neurological signs, and a rapid response to treatment with vitamin B_1. The rates of occurrence of the main manifestations in the 1942 group of patients is shown in Table II.

TABLE II.—SUBACUTE WET BERIBERI, MARCH TO JULY, 1942.

Incidence	Males	147	Age	0 – 20 years	8 cases
	Females	72		21 – 30	15
		—		31 – 40	48
	Total	219		41 – 50	60
				51 – 60	65
				over 60	23

= 8·7 per cent. of population.

Symptoms and signs

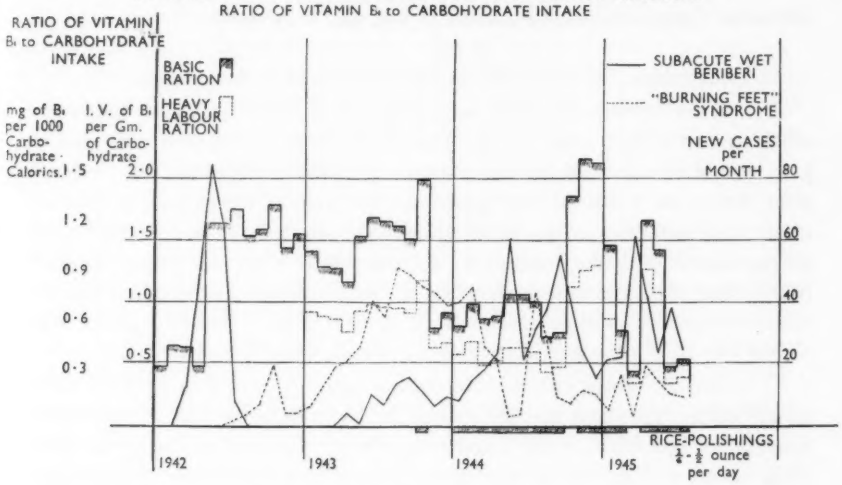
Œdema	Slight	37 – 16·9 per cent.	Weakness	None	10 – 4·6 per cent.
	+	154 – 70·3 per cent.		Slight	39 – 17·8 per cent.
	+ +	26 – 11·9 per cent.		Moderate	144 – 65·7 per cent.
	+ + +	2 – 0·9 per cent.		Severe	26 – 11·9 per cent.

Demonstrable Anæsthesia	Feet	98 – 44·7 per cent.	Paræsthesia	Feet	132 – 60·3 per cent.
	Hands	–		Hands	62 – 28·3 per cent.

Reflexes	Exaggerated	– Nil	Cardiac involvement		
	Normal	44 – 20·1 per cent.		Slight	17 – 7·8 per cent.
	Diminished	100 – 45·7 per cent.		Moderate	8 – 3·7 per cent.
	Absent	75 – 34·2 per cent.		Severe	1 – 0·3 per cent.

The onset was usually rapid, and followed an attack of acute bacillary dysentery in 55 per cent. of all dysentery cases (cf. Najjar and Holt, 1943). Severe cardiac involvement was happily uncommon and there were, in all, 13 deaths; multiple deficiency in other factors was present in the majority of fatal cases. In almost all cases there was tenderness of the calves and upon pressure over the main nerve trunks: wasting occurred but was often masked by œdema in the early stages. Most patients gained weight

GRAPH 2. CIVILIAN INTERNMENT CAMP, HONG KONG. 1942 - 1945.
INCIDENCE OF SUBACUTE WET BERIBERI AND "BURNING FEET" SYNDROME



at the onset—as much as 15 pounds in a week, but lost it rapidly when diuresis occurred as a result of treatment. Stiffness of muscles, loss of dexterity, constipation and abdominal distension were marked.

Response to treatment with synthetic vitamin B_1 was uniformly satisfactory except in the very few moribund cases who had many other deficiencies. At first an extravagant daily oral dose of 10 mg. was given and the average time of cure was 2·6 weeks; but later 2 to 10 mg. intramuscularly every day brought about cure in an average of ten days, with a great saving of material. A dietary supplement of bran or rice polishings, in the quantities which we were able to use (up to 1½ oz.), was only very slowly effective in mild cases. They were more useful for preventing relapse in patients who had been cured by synthetic vitamin B_1.

Chronic Dry Beriberi.

Six cases of this condition were seen. All had flaccid paraplegia, anæsthesia, wasting and absent reflexes in the legs. None had œdema, nor detectable cardiac abnormality. Treatment with pure vitamin B_1 parenterally brought about slow improvement and a return to normal in four to eight months. In 2 cases, who were under treatment when some Red Cross supplies arrived in 1944, improvement was considerably more rapid, when a synthetic B complex mixture was given by injection

than when B_1 was used alone. This B complex preparation contained, in addition to B_1 (5 mg.), riboflavine 0·2 mg., pyridoxine 5 mg., calcium pantothenate 5 mg., and niacin amide 25 mg. per 1 c.c. dose.

Sensory Neuropathy or "Burning Feet" Syndrome.

In the late summer of 1942, when the wet beriberi incidence had subsided to zero, there arose cases of a "peripheral neuropathy" in which pain and aberrations of sensation were the outstanding features. Thereafter, new cases continued to appear for the rest of the period of internment, the incidence curve being shown in Graph 2. Clearly there was no correlation with the vitamin B_1—carbohydrate ratio but it is noticeable that during the latter two years when the small addition of beans and bran raised the general level of intake of all factors of the B complex, there was a slow but steady decline in incidence. There were 756 cases.

The earliest symptoms in these cases were mild paræsthesiæ of the feet, described as "pins and needles," associated with aching which demanded movement but was largely unrelieved by it. Later the aching became more severe and spread up the legs to include the knee-joints, and sudden shooting pains, likened to electric shocks, were superadded. The paræsthesia became intense and often almost intolerable. It was usually described by sufferers as a sensation of "intense burning" or "freezing" of the feet. Pains were always worse at night and prevented sleep in most cases. In spite of the painful hyperæsthesia which was usually present most men got some kind of relief in walking about and all observers who have described the condition (Cruikshank, 1946; Jackson, 1946) recount the picture of numbers of these patients endlessly limping up and down between the huts through the hours of darkness.

Careful questioning of several hundreds of these men produced the conviction that, though some referred their aberrant temperature sensations to cold and others to heat and even obtained subjective relief from the appropriate application, a hot brick or cold water, all were interpreting in different ways the same sensation. Contrary to Jackson's experience, no change in skin temperature, nor evidence of vascular or vasomotor change could be detected.

In some cases anæsthesia of the soles developed, and two types of gait were distinguishable, the ataxia of plantar anæsthesia and the careful picking of the way, like a bather over shingle, of those with plantar hyperæsthesia.

Although physical signs were few and not alarming, the physical condi-

tion of these men deteriorated very rapidly and they suffered great loss of weight, as a result of exhaustion from pain and loss of sleep. None could do heavy labours on account of weakness, and their drawn, emaciated faces were suggestive of an advanced wasting disease.

Reflexes were exaggerated in the majority of early cases, but in later cases, who developed anæsthesia, reflexes diminished and were lost, ankle-jerk before knee-jerk, and in these latter there was weakness and some wasting, with complete single nerve paralysis in 6 per cent. of all cases.

As regards incidence; in the first two years males exceeded females in the proportion of two to one, but thereafter the sex incidence was equal. The age-incidence was exactly proportional to the distribution of age-groups in the population except that there were only two cases in children under 10 years old. Association with other B complex deficiencies is of some significance. Considering the cases of "burning feet" who were first seen in 1944 and 1945, 329 in number, no less than 261 (79·4 per cent.) also had evidence of nicotinic acid or riboflavine deficiency, or most commonly, both. This is in marked contrast to the findings among cases of wet beriberi, among 557 of whom, in the same period, only 83 (14·9%) had pellagrin or orogenital syndrome manifestations.

Similarly, in point of time, the incidence curve of "burning feet" bore no relationship to that of wet beriberi; a steep rise, in fact, occurring while prophylactic administration of synthetic B_1 was still being continued. On the other hand it showed the same general outline as the incidence curves for pellagra and orogenital syndrome, with a peak in autumn, 1942, a fall in the following winter, a large broad peak in the latter half of 1943 and early 1944, and a slow, steady decline from that time till mid-1945 (Smith, 1946), cf. Graph 3.

The response to treatment of the "burning feet" cases was disappointing but instructive.

Synthetic vitamin B_1 was used in all dosages from 1 to 200 mg. daily and given orally, hypodermically, intramuscularly, intravenously and even intrathecally. Of the 270 cases who had it for three months or more, only 17 per cent. were sufficiently relieved to stop attending for their injections and 55 per cent. were unimproved at all. 81 patients had B_1 injections for a year or more and all still complained of painful paræsthesiæ, though most had improved in strength and general condition.

The only other pure vitamin available was nicotinic acid. Given intravenously or on an empty stomach, a sufficiently large dose of this preparation to produce a marked "flush" gave temporary relief, but its prolonged administration had no permanent effect and the conclusion was reached

that its transitory effect was due solely to vasodilatation. In the winter of 1943 to 1944 the stock of B_1 was so low that it could only be given to patients in whom there was an immediate threat to life—e.g. cardiac cases, and its administration to "burning feet" cases stopped. However, within a few months small supplies of soya beans and rice polishings became available and enough of these were set aside to provide 1 to 2 oz. of each daily to this group. In addition they received 1½ oz. of "yeast," a fermented preparation brewed in the camp on a medium of flour, sugar and soya bean residue, and found effective in the treatment of ariboflavinosis. Slow but steady improvement was noted over the next six months and by the end of summer, 1944, all but 3 were back on heavy labour, though in a few cases patches of anæsthesia and diminished reflexes could be demonstrated a year later. The 3 resistant cases all improved rapidly on the "B complex synthetic injections" already referred to.

Nutritional Retrobulbar Neuropathy.

The first case of amblyopia was diagnosed in October, 1942, and thereafter the incidence occurred in two main waves—Graph 3. All age-groups and both sexes of the population were affected, though the condition was only diagnosed in 3 children of under 10 years of age—Table III.

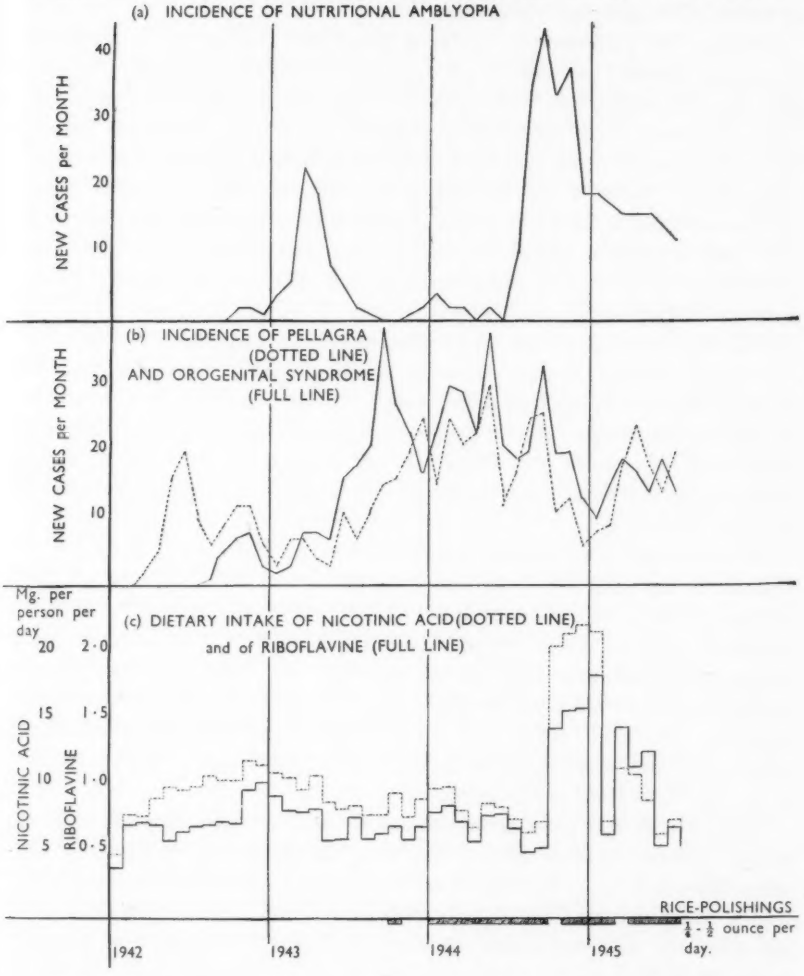
Table III.—Incidence of Nutritional Amblyopia.

Males	174 – 11·5 per cent.	Age 0 – 20	10 – 2·7 per cent.
Females	196 – 19·8 per cent.	21 – 30	40 – 11·1 per cent.
		31 – 40	97 – 16·1 per cent.
Total	370 – 14·8 per cent.	41 – 50	125 – 20·8 per cent.
		51 – 60	79 – 19·1 per cent.
		Over 60	19 – 12·8 per cent.

The outstanding symptoms were loss of visual acuity with disorders of perception, such as shimmering and flickering of images. Some degree of pain was present in 54 per cent. of cases and consciousness of a central blindspot was a spontaneous complaint in 24 cases (6·5 per cent.). Photophobia was not common and no corneal or conjunctival lesions were seen.

Upon examination there was some degree of visual impairment in all cases, though visual acuity was not a good guide to the severity of the condition, for patients soon learned to "look round" their scotoma by looking off-centre. Vision of less than 6/60 was found in only 22 (5·9 per cent.) cases, of whom 17 were men. A central or paracentral scotoma was found in all cases, larger for red than for black and white and there was constriction of the visual fields for colour discrimination.

GRAPH 3. CIVILIAN INTERNMENT CAMP, HONG KONG. 1942 - 1945.



Ophthalmoscopy, when possible, revealed degenerative pigment changes round the macula in 10 per cent. of patients and definite optic atrophy in 1 per cent. Temporal pallor of the disc was seen in about 25 per cent. but was of doubtful significance as it was also seen in a number of individuals who were entirely free of all symptoms and signs. Untreated, the condition progressed slowly and irregularly. Symptoms and

a scotoma had already been present for more than a year in the 3 cases in whom optic atrophy was definite.

Of the 370 patients who suffered from this condition, 79 (21·4 per cent.) had had wet beriberi, 38 (10·3 per cent.) had had pellagra, 145 (39·2 per cent.) "burning feet" and 143 (38·7 per cent.) orogenital syndrome. The first two of these are clearly insignificant as the proportion among the amblyopias is equal to or less than the proportion of the whole population who suffered from the respective diseases. On the other hand there does seem to be some connection between amblyopia and "burning feet" and orogenital syndrome, though the association between the two former was by no means as universal as was described by Durran (1946) and Garland (1946).

Possible extrinsic toxins were exhaustively investigated, but no common factor could be found. Tobacco can be excluded, as a proportion of patients (16·2 per cent.) had never smoked. The condition started in over 30 patients at a time when they were receiving daily B_1 injections for beriberi or for painful feet. The case incidence curve followed those for diseases due to B complex deficiencies, with a "lag" of about nine to twelve months, *see* Graph 3.

The response to treatment was similar to that of "burning feet." Pure vitamin B_1, nicotinic acid and vitamin A had no effect in any type of case. A small group of 15 were treated in October, 1944, with large doses of multivitamin capsules which arrived that month. These capsules contained riboflavine, pyridoxine and pantothenic acid in addition to vitamins A and B_1, and nicotinic acid, but there were only sufficient to continue treatment for a month. All the 15 cases except 1 improved but the experiment is so small and short as to have little significance. The improvement may have been psychogenic.

However, it was possible in the later years to supplement the diet of many of these patients with ground-nuts, beans, rice-polishings and the camp-brewed yeast. If this dietary addition could be maintained for several months it was found to prevent deterioration, and brought about improvement in some cases, the ratio of improved to stationary cases being about 4 to 3.

Discussion.

(1) *Subacute wet beriberi.*—This condition conformed to the classical descriptions and to the generally accepted views of its ætiology (Peters, 1936; Platt and Lu, 1936). The correlation between incidence of cases and the vitamin B_1—carbohydrate ratio was so close, the response to the treat-

ment with synthetic B_1 so constant and the effect of prophylactic administration so striking that, within the limits of the investigations possible, the condition could be regarded as a pure vitamin B_1 deficiency.

(2) *Chronic dry beriberi.*—The number of cases of this condition was too small for any definite conclusions to be justifiable. Clinically the cases were similar to those frequently seen among rice-eating peoples and there was a slow response to B_1. It is just worthy of note that cure was much more rapid when other B complex factors were provided as well, and it may be that some of these other factors contribute in some way to the causation. Similar conclusions were reached by Vilter, Blau and Spies (1942) and Spies, Bean and Asche (1939) who effected cure of symptoms resistant to thiamin in beriberi patients with adenylic acid and pyridoxine respectively.

(3) *The "burning feet" syndrome.*—There seems no doubt that this is the same condition as that described in association both with beriberi and with ariboflavinosis in many parts of the world. A review of this literature was given by Stannus in the Lumleian Lectures of 1944. The condition was also seen in the Spanish Civil War (Peraita, 1942). It is now clear, however, that the condition is not an essential part of either beriberi or ariboflavinosis, though frequently associated with either or both, and does frequently exist alone. Gopalan (1946) at Coonoor found in 53 cases exactly similar sensory manifestations to those discussed above, but very scanty objective signs, no weakness, no anæsthesia, and exaggerated reflexes in most cases. In the Hong Kong cases 35·4 per cent. had demonstrable anæsthesia and 35·0 per cent had diminished or absent reflexes. It is to be supposed that in these cases there was present some degree of chronic dry beriberi as a coexisting deficiency condition.

The results of treatment support this supposition to some extent for vitamin B_1 alone caused improvement but not freedom from pain in the same proportion (35 per cent.) of cases. Improvement of the "burning feet" themselves was produced by the dietary addition of beans, rice-polishings and yeast and it seemed to us that the condition must be caused by lack of some B complex factor or combination of factors, other than B_1 or nicotinic acid, and closely related to riboflavine. The work of Gopalan (1946) appears to have determined the identity of this factor, for, failing with B_1, nicotinic acid and riboflavine, he cured 53 cases of this condition with amazing rapidity by the daily injection of 40 mg. of calcium pantothenate. The finding of Burgess (1946) that the condition improved when the quantity of rice consumed was decreased without the diet being improved in any other way suggests that the requirement

of pantothenic acid depends on the carbohydrate intake and raises again the question of the ultimate mechanism by which this and other deficiencies produce their effect. The absence of any facilities for biochemical investigation made us unable to contribute in any way to the solution of this problem and the possibilities remain that impairment of cell function may be brought about by the simple insufficiency of some substance of catalytic nature derived from the vitamin (e.g. co-carboxylase in the case of B_1) or the toxic action of some abnormal product of imperfect metabolism (e.g. pyruvic acid or similar compounds, Walshe, 1941). Again we were unable to determine whether it is dietary insufficiency, failure of intestinal biosynthesis, or imperfect absorption or utilization alone which produce the effects; or whether some toxic factor, possibly present in rice, is involved either directly (Clarke and Sneddon, 1946; Kirman, 1946) or as a vitamin inhibitor (Clark, 1941).

(4) *Amblyopia or retrobulbar neuropathy.*—Impairment of vision with scotoma has been described frequently in association with "neuritic" beriberi (Elliott, 1920, and many Japanese writers), with pellagra (Stannus, 1912) and with ariboflavinosis (FitzGerald Moore, 1930; Landor and Pallister, 1935; Wilkinson and Au King, 1944); and in the course of the last year, many more cases have been reported, mostly from prison camps in the Far East, but also from the Near East (Spillane and Scott, 1945).

The exact ætiology of the retrobulbar neuropathy is still unknown. Arguments for vitamin B_1 deficiency (Dansey-Browning and Rich, 1946) and tobacco (Williamson, 1946) have been put forward, but experience in many camps (including that described above) has tended to show that tobacco as an ætiological factor can be ruled out and that there is no connection between the incidence of amblyopia and vitamin B_1 intake; nor can the condition be either prevented or cured by administration of large doses of pure B_1 over long periods. Nicotinic acid and vitamin A have similarly proved ineffective in treatment, though this cannot be taken to prove that they have no connection with the condition.

On the other hand the relationship of the incidence of the condition to the level of intake of B complex generally and to the incidence of known B complex deficiency states, together with the promising results of treatment in the camps and after release with substances rich in B complex, beans, rice-polishings, yeast on the one hand, liver extract and marmite on the other (Livingston, 1946; Ridley, 1946), do suggest that lack of an unidentified factor or combination of factors of that complex may be the cause of the condition.

But while all the relatively successful therapeutic agents in nutritional amblyopia cases are good sources of B complex vitamins, they are also good sources of protein; and on the above grounds it can equally well be postulated that an essential amino-acid is the missing factor—an amino-acid which is present in these substances but was absent from the normal camp diets.

Summary.

Four diseases affecting the nervous system, and apparently due to dietary deficiency, are described as they occurred in the Civilian Internment Camp, Hong Kong, 1942 to 1945.

(1) Subacute wet beriberi—844 cases, conformed to previous descriptions and, in respect of incidence, prevention and treatment, was apparently due to a pure vitamin B_1 deficiency. The threshold vitamin B_1—carbohydrate ratio was found to be about 0·4 mg. per 1,000 carbohydrate calories.

(2) Chronic dry beriberi—small number of typical cases responded slowly to treatment with vitamin B_1, but more rapidly to whole vitamin B complex.

(3) "Burning feet" syndrome—756 cases, in 35 per cent. of which dry beriberi was superimposed, were found to show no response to vitamin B_1 or nicotinic acid but to be slowly cured by food rich in vitamin B complex, the individual factor responsible being probably pantothenic acid.

(4) Amblyopia—370 cases, in which central or paracentral scotoma was the outsanding feature, was generally associated with B complex deficiencies and showed some response to foods rich in these factors, though on the present evidence the causative deficiency might equally be of an essential amino-acid.

I wish to express my gratitude to numerous fellow-internees whose co-operation made the collection of this material possible; to Sir Lionel Whitby, C.V.O., Regius Professor of Physic, University of Cambridge, for permission to reproduce Graphs 1 and 2; to Dr. B. S. Platt, C.M.G., for his help and advice and the hospitality of the Human Nutrition Research Unit; and to Dr. A. Wilson Rae, C.M.G., Deputy Medical Adviser to the Colonial Office, and Dr. P. S. Selwyn-Clarke, C.M.G., Director of Medical Services, Hong Kong, for permission to publish this paper.

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MENINGITIS CARCINOMATOSA: A REPORT ON TWO CASES.

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THE term meningitis carcinomatosa was first used by Siefert (1901 and 1903) and later adopted by other authors to describe carcinomatous infiltration of the leptomeninges. Earlier writers recognized the syndrome but followed Oppenheimer's suggestion (1888) that the cerebral symptoms were due to the action of toxins produced by a visceral carcinoma, although Eberth (1870) had described secondary invasion of the leptomeninges in a case of tumour of the lung. To Saenger (1900) and Lilienfeld and Benda (1901) goes the credit of correlating the infiltration of the leptomeninges with the primary growth elsewhere.

Since then approximately 40 cases have been reported. An exact evaluation of this number is complicated by some authors' confusion of this condition with carcinomatous invasion of the dura, which has been shown by Russell and Cairns (1934) to be a chronic intradural hæmatoma due to multiple blood-borne metastases.

Full pathological descriptions of the invasion of the leptomeninges were published in Germany by several authors including Schwarz and Bertels (1911). Recently cases have been described in most countries including 3 cases in the British Isles (Walshe, 1923; Moorhead and Wigham, 1926; and Greenfield, 1938).

Clinically the cases of meningitis carcinomatosa appear to fall into three groups:

(I) With slow development of symptoms, suggestive of a cerebral tumour.

(II) With involvement of the spinal and basal meninges, of which we have traced 3 cases, Rehn (1906), Heyde and Curshmann (1906), and Alpers and Smith (1938).

(III) With a rapid course resembling leptomeningitis; this group includes 27 recorded cases (*see* references) and our 2.

Case 1.—J. C. B., male factory worker, aged 34, admitted November 7, 1944, to Warrington General Hospital under care of G. J. D. The patient had been in bed at home for three weeks complaining of headache, pains down the back, drowsiness

and occasional vomiting, following a cold in the head. On admission the patient was drowsy and apathetic, but answered questions readily. He looked somewhat emaciated, said he had been losing weight during the last two or three months and had no appetite. His tendon-jerks were extremely difficult to elicit. Kernig's sign was present bilaterally but there was no neck rigidity.

An unusual feature was the constant production of severe pain in left shoulder when eliciting Kernig's sign on that side; the patient later said he had noticed numbness on the outer side of his left arm and hand. No objective sensory loss was demonstrable till November 24 when he was found to have lost appreciation of pin-prick over the little and ring fingers and outer portion of the left arm.

Headache and vomiting became more severe and his condition steadily deteriorated. On November 17 neck rigidity appeared and subsequently muscular tone and power became so reduced that the patient could hardly lift his limbs. He died on November 27, having been ill in bed for approximately forty days.

While the patient was in hospital his temperature tended to be subnormal (97° to 97·4° F.) and his pulse-rate 64 to 92 per minute. The urine was normal throughout. The blood-count showed no abnormality.

Cerebrospinal Fluid.

Date	9.11.44	18.11.44	22.11.44
Pressure	Not recorded	Not recorded	Over 300 mm.
Appearance	Cloudy, colourless	Cloudy, colourless	Cloudy, colourless
Globulin	Marked increase	Marked increase	Marked increase
Protein	350 mg. per cent.	500 mg. per cent.	600 mg. per cent.
Glucose	50·8 mg. per cent.	44 mg. per cent.	
Chlorides	630 mg. per cent.	660 mg. per cent.	640 mg. per cent.
Cells per c.mm.	11 lymphocytes	10 lymphocytes	8 lymphocytes

Autopsy on November 27 confirmed the muscle wasting. The apex of the right lung showed a little scarring. There were three or four hard nodules of dark tissue situated in the left lung, just below the pleura and there were numerous large, hard hilar and mediastinal glands.

The stomach was small and contracted, almost "leather bottle." On the lesser curvature there was a smooth white, raised, hard, umbilicated, nummular area about 4 cm. across by 1 cm. thick. This appeared to fade imperceptibly into the adjacent gastric muscle and mucosa. Two hard lymph-glands, each about 1·3 cm. across, were adherent to the serosa underlying the growth and there were several others along the lesser curvature. Two similar glands adjoined the common bile duct. The kidneys showed macroscopic evidence of chronic nephritis. The dura mater appeared unusually tense, there was an increase in the amount of cerebrospinal fluid, and the arachnoid over the interpeduncular space was more opaque than normal; otherwise there was no macroscopic abnormality of the meninges nor of the surface of the brain.

Microscopical examination.—Sections verified the existence of a scirrhous gastric carcinoma. The cells occurred singly or in small groups; they were large, hyperchromatic, the nucleus round or crescent-shaped and often pushed to one side of the cell; the eosinophilic cytoplasm contained a vacuole placed opposite the concavity of the nucleus; some cells appeared swollen and the vacuole was interpreted as being mucin. All coats of the stomach and all the lymph nodes were invaded. There were numerous emboli of carcinoma cells in the lymphatics.

Sections taken at various levels of the spinal cord showed infiltration of the leptomeninges by carcinoma cells resembling those in the stomach. They lined the

arachnoid spaces, replacing the meningeal cells, and on the scaffolding of the meningeal meshwork they formed a thin carcinomatous mantle, slightly thicker posteriorly. In places they occurred as compact groups of cells, reproducing the appearance of the emboli seen in the gastric lymphatics. The perineural spaces were infiltrated and the malignant cells followed the lines of the supporting tissue and sometimes lay between the medullated fibres (figs. 1 and 2, Plate XXVII). Longitudinal sections of the entering posterior nerve-roots showed carcinoma cells accompanying the nerve-fibres till they entered the cord, where the malignant cells came to an abrupt stop. No inflammatory reaction was seen.

In view of the symptoms it was surprising that the infiltration ceased at the lower level of the medulla oblongata.

Case 2.—J. A. C., a male clerk, aged 49, admitted February 5, 1946, to Emergency Hospital, Winwick, under care of A. S. K. He had been in bed for three weeks altogether, at home and in Preston Royal Infirmary, complaining of headache and vomiting. His past health had been good except that he had noticed transitory swellings of portions of his limbs a few months previously. On December 26 he suffered a sudden attack of confusion and vertigo. This was followed by headache and on one occasion by a profuse nasal discharge. About January 24 deterioration of speech and memory was noticed. When admitted on February 5 he was flushed, obviously in pain, confused and had a mixed aphasia; there was marked rigidity and Kernig's sign, and possibly a right facial paresis. A blood-count and examination of the urine did not reveal any abnormality.

His condition varied from day to day till on February 23 he suddenly became comatose. For this reason ventriculography was performed revealing a slight symmetrical dilatation of all four ventricles and an intracranial pressure greater than 300 mm. of water. The cerebellum was explored to exclude an abscess. Following this manipulation the temperature rose to 100·4° F. and patient died on February 24. He had been confined to bed for approximately forty days.

While the patient was in hospital his temperature was virtually normal. Before the terminal pyrexia it was twice recorded as 99° and once as 101° F. His pulse-rate varied between 68 and 118 but was usually below 90.

At first the possibility of tuberculous meningitis was considered and the patient was given 40 c.c. of promanide on February 7 and 8. Later the scanty growth of a staphylococcus from one specimen of cerebrospinal fluid led to the administration of 180,000 units of penicillin intrathecally and 420,000 units by the intramuscular route between February 8 and 11. From February 11 to 23 30 grains of potassium iodide were prescribed four-hourly together with a course of sulphadiazine because of the suspicion that the large cells in the cerebrospinal fluid might be those of a fungus.

CEREBROSPINAL FLUID.

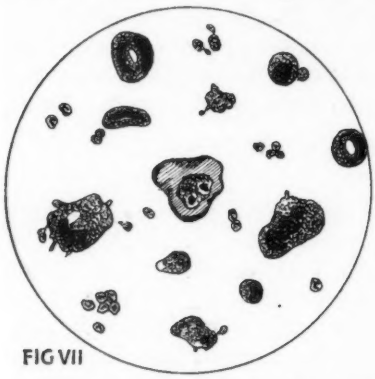
Date	29.1.46	5.2.46	6.2.46	9.2.46
Pressure ..	400+	Not recorded	Not recorded	Not recorded
Appearance ..	Clear	Colourless, cloudy	Colourless, cloudy	Colourless, cloudy
Globulin ..	—	—	—	—
Protein	50 mg. per cent.	140 mg. per cent.	80 mg. per cent.	70 mg. per cent.
Glucose ..	—	—	—	—
Chlorides ..	720 mg. per cent.	700 mg. per cent.	700 mg. per cent.	680 mg. per cent.

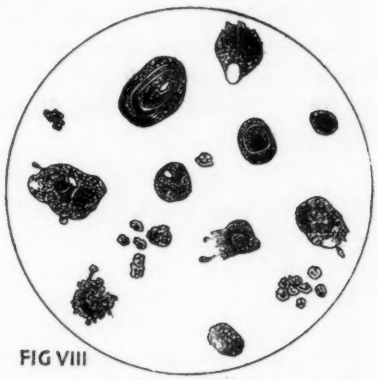
Date	29.1.46	5.2.46	6.2.46	9.2.46
Kahn	—	Negative	—	—
Gold	—	—	—	—
Cells per c.mm.	53	250	245	894
Polymorphs ..	21	22	44	Difficult to differentiate
Small cells ..	32	163	103	
V. large cells ..	—	66	98	
Culture ..	—	A few staphs. on subculture	—	Sterile

Date	9.2.46	10.2.46	14.2.46	23.2.46
Pressure ..	Not recorded	Not recorded	160 mm. H_2O	Much above 300 mm. H_2O
Appearance ..	Yellow opaque	Yellow opaque tiny flakes	Pale yellow, sl. cloudy	
Globulin ..	—	—	—	Negative
Protein	70 mg. per cent.	—	90 mg. per cent.	15 mg. per cent.
Glucose ..	—	—	34 mg. per cent.	—
Chlorides ..	—	—	620 mg. per cent.	—
Kahn	—	—	—	—
Gold	—	—	—	—
Cells per c.mm. ..	265	757	245	15
Polymorphs ..	30	Difficult to differentiate	Similar types, difficult to differentiate	
Small cells ..	223			
V. large cells ..	12			15
Culture ..	Sterile (Penicillin content : 10 units per c.c.)	A few diphtheroids on subculture	—	

Note on cerebrospinal fluid of Case 2.—In the wet films of the cerebrospinal fluid, besides the usual grey transparent leucocytes that spread out on the glass of the counting chamber, there were great numbers of large, opaque, pale green cells that remained spherical. Some were as large as 65μ in diameter. For two hours these cells were watched and were seen to produce buds, some of which broke off, the appearances suggesting fungus or protozoon. Stained with hæmatoxylin and eosin the large cells (figs. 7 and 8) showed cloudy, frothy, eosinophilic cytoplasm and large crescentic, coarsely vesicular nuclei with one or two eosinophilic nucleoli. The nucleus was generally situated laterally, often forming a bulge on the surface of the cell. In the swollen cytoplasm there was a vacuole occupying one-third to two-thirds of the cell which consequently had a signet-ring appearance. Saucer-shaped, round, ovoid and necrotic nuclei were seen and some of these showed mitotic figures. Ziehl-Neelsen staining showed the nuclear arrangement clearly; some of

the cells had two or more nuclei; the outermost was shaped like a skull-cap and lay against the periphery of the cell. The second nucleus lay within the concavity of the first with its long diameter set obliquely: the third and subsequent nuclei were similarly placed, the whole looking like a heap of precariously piled saucers. The fact that they were carcinoma cells was not recognized at this time.





FIGS. 7 and 8 (*Case* 2).—Carcinoma cells and a few polymorphonuclear cells from cerebrospinal fluid. ×550.

Hæmatoxylin staining also demonstrated the large range in size of the malignant cells, differentiating polymorphonuclears from small carcinoma cells, and cast-off cytoplasm from small lymphocytes. These distinctions were difficult to make in the counting chamber.

Autopsy on February 25, 1946, revealed a large fleshy prepyloric gastric ulcer with thick edges and base and extensive upper peritoneal adhesions. The brain and leptomeninges were normal except for ventricular dilatation and a few groups of minute white spots on the cortex. There was also a milkiness of the pia-arachnoid in the velum interpositum and in the Sylvian fissures which was more marked along the vessels.

No secondary growths were found in the lungs or liver and lymphatic involvement was not apparent.

Microscopical examination.—In the gastric ulcer the malignant cells were extremely large and almost exactly resembled those seen in the cerebrospinal fluid. They invaded all coats, but provoked virtually no fibrous reaction. They formed numerous emboli in the lymphatics; in places they surrounded the nerves but none were demonstrable in the perineural canals or blood-vessels. The lung sections showed only bronchopneumonia.

The appearance of the leptomeninges was even more striking than in Case 1. All portions of the cerebral meninges available for examination were heavily invaded by cancer cells similar to those seen in the gastric wall and spinal fluid (fig. 6). To quote Boyd's description "the sub-arachnoid space was filled with cells that invaded every nook and cranny of that space. It was as if molten wax had been poured into the space and had then been allowed to solidify" (fig. 3). Occasionally in the thicker sheets there was a small patch of carcinoma cells with necrotic nuclei. There was no inflammatory reaction. Perivascular infiltration of the cerebrum and cerebellum was observed to a depth of about 0·2 mm. (figs. 4 and 5).

Discussion.

In studying the descriptions of histological changes in 43 previously published cases of meningitis carcinomatosa, one is struck by the uniformity of the microscopic picture, which is largely independent of the clinical condition and the site and nature of the primary growth. The appearances are the same with primary tumours as diverse as carcinoma of stomach, lung and breast and melanoma, epithelioma and teratogenous carcinoma.

In some cases where the condition is less rapidly fatal the cells infiltrating the perivascular spaces penetrate the brain substance, giving rise to cerebral degeneration and hæmorrhage (Heinemann, 1911; Lewis, 1925); in others the malignant process in the pia results in erosion of the brain surface (Walshe, 1923; Albrecht, 1932) and the choroid plexus and ependyma may be involved (Bertrand and Aronson, 1921). Infiltration about the nerve roots may result in macroscopic nodules. Perivascular infiltration into the cord itself has not been described.

The mode of origin of this subarachnoid infiltration has been discussed by Key and Retzius (1870), Weed (1914), Hassin (1919) and Morse (1923). They consider that it is due to spread via lymphatics and tissue spaces which communicate with the perineural spaces and in turn make connection with the subarachnoid space. Morse describes malignant cells infiltrating the perineural spaces of the gastric nerves. Once the malignant cells have reached the subarachnoid space further spread seems to depend on mechanical factors such as the configuration of the space and the action of gravity. Crevices are filled, the vertex is apt to have a thinner layer than the base, the posterior aspect of the spinal cord is usually more heavily infiltrated than the anterior. This infiltration may be much more extensive than the physical signs would suggest. In Walshe's case

(1923) the base of the brain and the trigeminal nerve were infiltrated with no symptoms referable to them. Cornwall (1927) and Albrecht (1932) found no symptoms referable to the seventh cranial nerve, even though this nerve was found post mortem to be infiltrated.

Carcinoma cells in cerebrospinal fluid are not often described, nevertheless they were reported in 8 of the 27 cases where meningitis carcinomatosa resembled leptomeningitis and in one case of slower development (Peter, 1924). This does not include 3 cases where the authors were doubtful as to the nature of the cells, nor a further 3 where the cells were found in fluid withdrawn only after the death of the patient.

There is a close resemblance between these descriptions and that of the cells recovered in Case 2. Most authors, like ourselves, found that since the fluid did not clot they were able to obtain the cells from the sediment. All note the great size of the cells. Schwarz and Bertels (1911) state they are 10 to 15 times the size of lymphocytes: and Wullenweber (1923) gives five times the diameter of polymorphs. The "signet-ring" appearance on staining with hæmatoxylin, and the peculiar nuclear arrangement in the multinucleate cells are outstanding features. This uniformity holds when the condition is secondary to growths in the stomach (Stadelmann—2 cases—1908; Schwarz and Bertels, 1911; Wullenweber, 1923), lung (Peter, 1924; Bertha—2 cases—1935) and breast (Humbert and Alexieff, 1913).

In Boyd's case (1925) where the primary growth was a malignant melanoma of the skin he describes the cells as "unlike any he had hitherto seen," with large pale oval eccentric nuclei and abundant cytoplasm.

The number of malignant cells present in the fluid varies widely, from a few cells to several hundred per cubic millimetre.

It is not clearly brought out in the accounts whether the carcinoma cells were recognizable as such when seen in the cerebrospinal fluid, or whether their nature was inferred only after the primary growth had been correlated with the cerebral symptoms, either during life or post mortem. We think that although the cytology on hæmatoxylin staining is suggestive it is unwise to dogmatize on the nature of suspected carcinoma cells recovered from the cerebrospinal fluid unless other features of the case are consistent.

Diagnosis.

As said above, the more slowly fatal cases (Group I) mimic cerebral tumours in their symptomatology. From study of their protocols it would appear that the cerebral condition is usually recognized as secondary

to a growth elsewhere and the case is only regarded as exceptional when no metastases are seen in brain substance post mortem.

The spinal and basal type (Group II) mimics polyneuritis with a short terminal meningitic phase. It is interesting that our Case 1, which was pathologically an example of Group II, clinically belonged to Group III. We regard these last two groups as merging imperceptibly one into the other.

The more rapidly fatal type (Group III) resembles leptomeningitis except that it is usually afebrile. We have heard of a few other cases and wonder if meningitis carcinomatosa is as rare as commonly supposed. Its infrequent recognition is possibly because the macroscopic changes are slight, milkiness of the meninges is often only a matter of opinion, so unless these membranes are examined microscopically no evidence will be forthcoming. In this connection it is well to emphasize that the carcinomatous invasion may be confined to the spinal meninges, viz. Alpers and Smith (1938). The possibility of meningitis carcinomatosa might be considered in any obscure case of meningitis or polyneuritis in the adult, when the illness is grave and there is little or no fever. As in over one-quarter of the published cases the victims were men between the ages of 20 and 40 it is not surprising that symptoms such as anorexia and loss of weight were not correlated with malignant disease.

Lumbar puncture may yield much valuable information. In all cases where the manometric pressure was recorded it was found to be raised. The most characteristic change in the fluid is an increase in the protein content, which in Bertrand and Aronson's case (1921) reached 1020 mg. per cent. In some cases cancer cells are seen in the fluid and if meningitis carcinomatosa is not suspected, they may pass unrecognized, but the cytology becomes clearer on hæmatoxylin and eosin staining. In most observations there has been a moderate increase in the white cell count, which is usually about seven to twelve per c.mm., though it may be as high as several hundred, when lymphocytes predominate. The sugar and chloride content of the cerebrospinal fluid may be misleading as they sometimes drop to levels usually associated with tuberculous meningitis. However the almost constant absence of the fibrin clot so characteristic of tuberculous meningitis should prevent confusion.

Another feature in carcinomatous meningitis is the frequency with which the pathological process picks out certain cranial or spinal nerves or an individual area of the brain, causing local pain followed by loss of function. This point was well illustrated in Case 1 by the local involvement of the left cervical nerves, which first caused pain in the left shoulder

when the meninges were stretched as in eliciting Kernig's sign, followed by paræsthesiæ and anæsthesia in the distribution of the sixth and seventh cervical nerves. Pain in the hip and weakness and numbness of the limbs and involvement of cranial nerves have been mentioned by others. The aphasia and right facial weakness in Case 2 were presumably due to early involvement of the left temporal region of the cortex.

Despite the presence of a primary lesion elsewhere, it may not be possible in these acute cases to obtain any evidence of this from the history or physical signs.

SUMMARY.

(1) Two cases of carcinomatous invasion of the leptomeninges are described and the differential diagnosis is discussed.

(2) Only 3 similar cases have been reported in the British literature and about 41 elsewhere.

(3) Meningitis carcinomatosa is possibly more common than is generally supposed.

(4) Methods for its recognition are suggested.

We wish to thank Dr. Raymond Whitehead of the Department of Pathology, Manchester University, for his constructive criticism and help with this paper; Dr. William E. Bowden, Police Surgeon to the County Borough of Warrington, for allowing one of us (G. J. D.) to attend the post-mortem of Case 1, and giving us the complete brain and spinal cord and other specimens; Dr. John Ferguson of the Warrington General Hospital; Dr. Hanna Rudolfer and Dr. M. Kutner for help with the German articles; Miss Ruby Easton, Technician at the Winwick E.M.S. Laboratory, for the drawings of the cancer cells in the spinal fluid; and the Library Staff of the R.S.M. for their help in tracing the references.

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PLATE XXVII (*Opposite*).

FIG. 1 (*Case* 1).—Spinal nerves surrounded by infiltrated meninges. ×40.

FIG. 2 (*Case* 1).—Showing infiltration of carcinoma cells between the nerve bundles. ×200.

FIG. 3 (*Case* 2).—Infiltration of cerebellar meninges by carcinoma cells. ×40.

FIG. 4 (*Case* 2).—Perivascular spaces of cerebral cortex invaded by carcinoma cells from the meninges. ×45.

FIG. 5 (*Case* 2).—Carcinoma cells lying in perivascular space. ×200.

FIG. 6 (*Case* 2).—Carcinoma cells in meninges. ×200.

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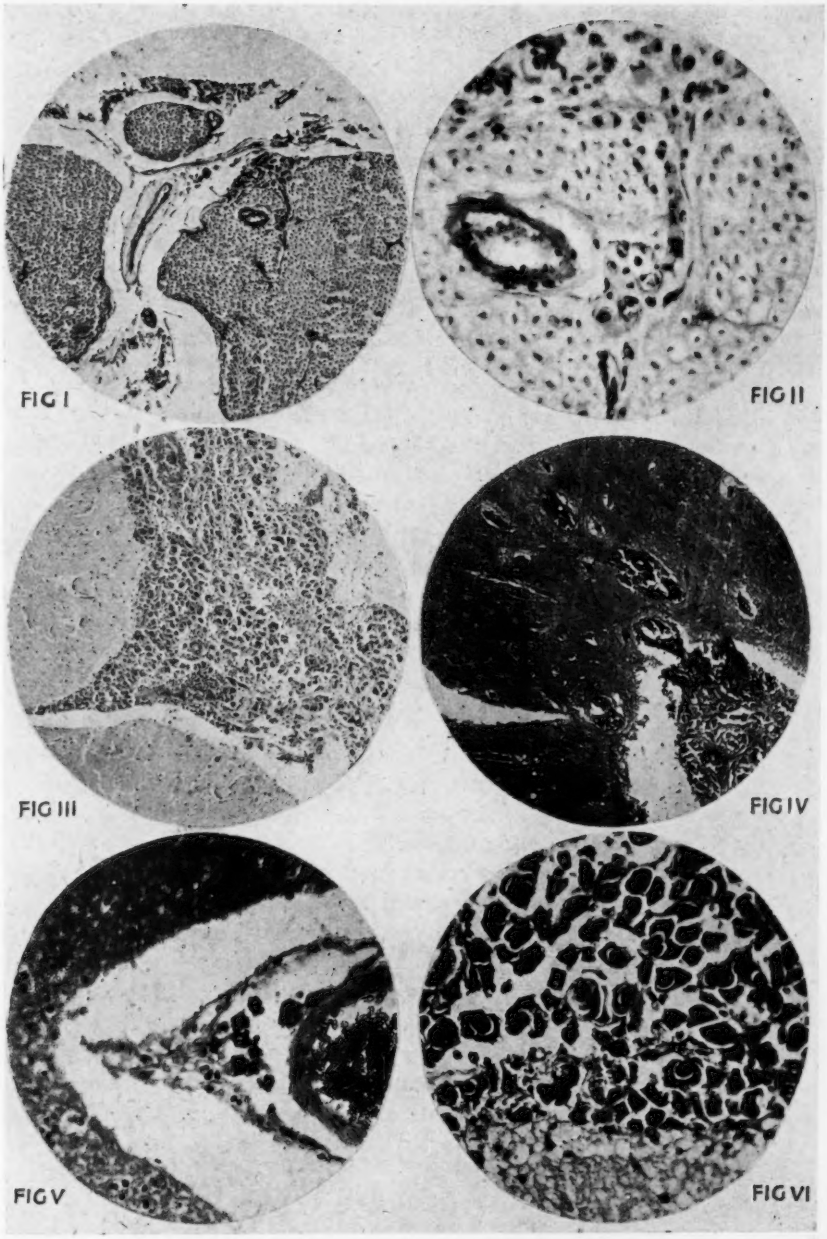
PLATE XXVII.



To illustrate article by G. Joly Dixon, Alan Sutcliffe Kerr and Mary E. Sharp.